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Ambient Water Quality Criteria: Cadmium

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CADMIUM

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
Washington, D.C.

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CRITERION DOCUMENT

CADMIUM

CRITERIA

Aquatic Life

For cadmium the criterion to protect freshwater aquatic life as derived using the Guidelines is $e^{(0.87 \ln(\text{hardness}) - 4.38)}$ as a 24-hour average (see the figure "24-hour average cadmium concentration vs. hardness should not exceed $e^{(1.30 \ln(\text{hardness}) - 3.92)}$ (see the figure "maximum cadmium concentration vs. hardness") at any time.

For cadmium the criterion to protect saltwater aquatic life as derived using the Guidelines is 1.0 µg/l as a 24-hour average and the concentration should not exceed 16 µg/l at any time.

Human Health

For the protection of human health from the toxic properties of cadmium ingested through water and through contaminated aquatic organisms, the ambient water criterion is determined to be 10 µg/l.

BIBLIOGRAPHIC INFORMATION

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Criteria and Standards Div.

Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for cadmium. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no r, ...

KEYWORDS: *Water quality, *Toxicology, *Cadmium, *Water pollution effects(Humans), *Water pollution effects(Animals), *Toxic substances.

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Introduction

Cadmium is a soft white metal which dissolves readily in mineral acids. It is used in electroplating, paint and pigment manufacture and as a stabilizer in plastics manufacture (Fulkerson and Goeller, 1973). The solubility of cadmium compounds in water depends on the nature of the compounds and on water quality. However, in most situations sufficient cadmium can be dissolved to cause toxic effects to aquatic organisms (Baes, 1973). Cadmium ion is precipitated from solution by carbonate, a hydroxide and sulfide ions (Baes, 1973) and forms soluble complexes with other anions (Samuelson, 1963). Most freshwaters in the United States contain less than 1 µg/l of cadmium, although levels as high as 120 µg/l have been reported (Kopp and Kroner, 1967).

Cadmium reaches waterways as fallout from air and in effluents from pigments, plastics, alloys and other manufacturing operations as well as from municipal effluents. Cadmium is strongly adsorbed to clays, muds, humic and organic materials and some hydrous oxides (Watson, 1973), all of which tend to remove it from the water column by precipitation.

In the aquatic environment, cadmium is acutely toxic to fish at concentratitons as low as about 1 ug/l (Eaton, In Press; Carroll, et al. 1979). Chronic toxicity to fish has been reported at approximately the same levels (Sauter, et al. 1976). Water quality also affects cadmium toxicity independent of its effect on solubility. Tabata (1969) and Carroll, et al. (1979) have shown that in acute tests calcium ion protects fishes against cadmium toxicity. Cadmium has been reported to bioconcentrate in fish tissues to levels 2,000 times as great as those of ambient waters (Spehar, 1976). Since cadmium is an element, it will not be destroyed and may be expected to persist indefinitely in the environment in some form.

Cadmium tends to accumulate in liver and kidney of exposed organisms. In humans the threshold for kidney dysfunction is about 200 mg/kg in the renal cortex (Friberg, et al. 1974). Cadmium has been identified as a cause of Itai-itai disease in Japan and has been implicated as a mutagen and carcinogen (42 FR 56575, October 26, 1977).

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

Cadmium is a common component of natural freshwaters and can occur at extremely low concentrations (less than 0.01 µg/l). In environments impacted by man, total cadmium concentrations can be several micrograms per liter or greater. The determination of the significance of total cadmium concentrations with respect to possible adverse effects on aquatic life can be complicated. For example, there are a variety of possible chemical forms of cadmium in natural waters which may display different toxicity or bioaccumulation in addition to substances causing synergistic and antagonistic effects.

In regard to the latter case, hardness components, common to all natural waters, are known to act antagonistically with cadmium to reduce toxicity. Therefore, by expressing toxicity as a function of both cadmium concentration and hardness (see Figures labeled "24-hour average cadmium concentration vs. hardness" and "maximum cadmium concentration vs. hardness"), the ability to derive criteria for freshwater organisms is significantly improved.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] and the Methodology Document in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

Attempts to measure one or more of the forms of cadmium in freshwater toxicity tests have rarely been made. However, first-approximations of cadmium's water chemistry can be obtained by knowing the total cadmium concentration, pH, total calcium, total magnesium, and total alkalinity (total carbonate species) of the test water. This may then be used to estimate possible cadmium carbonate precipitation. In the case of cadmium, complex formation by common anions (e.g., chloride, sulfate) in well-oxygenated fresh water is relatively weak. It is only when concentrations of these components become high (e.g., $10^{-2}M$) that a large portion (approximately 1/2) of cadmium is complexed. Since these conditions should not be common in toxicity testing, free cadmium (Cd^{2+}) is the predominant dissolved species. This applies to waters with low total organic carbon and the absence of other less prevalent but relatively strong complexing agents, such as aminopolycarboxylic acids.

If it is assumed that complex formation and precipitation reactions involving carbonate and hydroxide are probable equi-libria governing free cadmium concentrations for toxicity test waters, application of such a model provides a useful first estimate of whether cadmium carbonate or cadmium hydroxide species are possible in a particular system. As a result, the relationship for total dissolved cadmium and total precipitated cadmium may be written:

(1) total dissolved cadmium = $(Cd^{2+}) + (CdOH^{+}) + (CdCO_3)$

(2) total precipitated cadmium = $(CdCO_3)_x$

Based on reasonable assumptions and the use of known equilibrium constants, several other reactions have been eliminated. For example, it can be readily calculated that cadmium hydroxide precipitation should only begin in the vicinity of pH 10 to 11 with relatively high total cadmium concentrations. Therefore, it follows that cadmium hydroxide precipitation should usually not occur under natural toxicity testing circumstances--thus making the reaction relatively umimportant. Furthermore, cadmium concentrations of approximately 1 ug/l and below probably will not precipitate as cadmium carbonate, provided that the approximate limits of pH 8.5 and total carbonate of 10^{-2}M--usually near the maximum for natural waters--are not exceeded.

For saltwater test systems with typical salinity, the number of probable cadmium species is reduced to a few. Cadmium chloride complexes are predicted to predominate.

The rate at which a precipitate is formed can be somewhat unpredictable. Application of the model is particularly useful for the case of determining when precipitation by carbonate will likely not occur. Under defined cases of high cadmium concentration, high alkalinity, and high pH, equilibrium calculations can be expected to be useful in predicting whether precipitation will occur. While keeping in mind such limitations, these considerations can be of aid in determining possible forms of cadmium in test systems.

The following data on the effects of cadmium (Tables 1-7) represent appropriate information from the past and current literature. However, there is a limited knowledge of the importance of the various processes involving cadmium in natural waters such as adsorption, precipitation, complexation, and bioaccumulation in addition to effects these processes may have on changing the toxicity of cadmium.

Acute Toxicity

Examination of LC50 values for fish (Table 1) shows concentrations, adjusted only for differences in toxicity test methods, ranging from a low of 0.55 µg/l to a high of 40,182 µg/l, with several intermediate values showing intraspecific variability, possibly due to water quality effects (Pickering and Gast, 1972). Although some of the adjusted LC50 values appear relatively low, there is credence in the fact that four independent studies (Chapman, In press; Hale, 1977; Davies, 1976; Kumada, et al. 1973) present values below 10 µg/l, which is the maximum allowable cadmium concentration for potable water in the United States. It should be noted that there is a relatively large difference between data from Rehwoldt, et al. (1972) and Hughes (1973) for striped bass tested at about the same hardness. There are few LC50 data for salmonids in harder waters, although Davies (1976) (Table 7) found rainbow trout considerably less sensitive in hardwater than in softwater with a 96-hour LC20 of 20 µg/l at a hardness of 326 mg/l. In accord with these low acute values are the somewhat longer term acute mortality data of Chapman (In press) and Chapman and Stevens (In press) in Table 7. Almost all of their LC50 and LC10 values, approximately 200- to 400-hour tests, were relatively low.

The toxicity data in Table 1 indicate that water hardness significantly influences the acute toxicity of cadmium to fish.

Following the Guidelines, an exponential equation describing the relationship of toxicity to hardness for each species was fit by least squares regression of the natural logarithms of the toxicity values and hardness.

For cadmium, sufficient acute toxicity data and hardness ranges were available for four (4) fish species to fit regression equations. The slope of these equations ranged from 1.01 for green sunfish to 1.63 for goldfish, with a mean of 1.30.

As a measure of relative species sensitivity to cadmium, logarithmic intercepts were calculated for each species by fitting the mean slope (1.30) through the geometric mean toxicity value and hardness for each species. These intercepts varied from -3.92 for rainbow trout to 4.30 for mosquitofish, with a mean intercept of 1.20 for all 16 fish species. This variation in logarithmic intercepts indicates a range of species sensitivity to cadmium of 3,700 fold, even when adjusted for hardness effects. Even after the mean intercept (1.20) is adjusted by the species sensitivity factor of 3.9, rainbow trout and three other species have lower intercepts, i.e., are more sensitive. Since rainbow trout had the lowest intercept based on the results of flowthrough tests with measured concentrations, the Final Fish Acute Value is derived using the geometric mean slope (1.30) and the intercept for rainbow trout (-3.92).

Variation observed for invertebrate acute values is seen to be nearly as great as the acute data on fish; the adjusted invertebrate LC50 range is 3.8 to 28,000 µg/l. However, there also was a relatively more narrow range of hardness in the toxicity test waters (10 to 81 mg/l) as compared to the fish acute tests (10 to 360 mg/l). Few flow-through tests have been conducted with invertebrate species. Cladocerans, such as Daphnia magna, were the most sensitive species and mayflies and stoneflies were the most resistant. However, insects and many other invertebrate species are more sensitive when they molt, an event not usually occurring among most individuals (daphnids and copepods excepted) in 2- to 4-day toxicity tests. Only in the work of Giesy, et al. (1977) with cladocerans are LC50 values below 10 µg/l. Particularly noteworthy is their work suggesting changing toxicity as a function of introducing different sources of natural organic material capable of complexing cadmium. Although relatively little is reported on this subject at the present time, it is reasonaable to assume that various forms of cadmium in polluted waters, besides the free form, may be factors in causing toxicity. No data were available to indicate hardness effects on acute toxicity to invertebrate species since no species has been tested over a range of water hardness. Assuming that a similar relationship to hardness probably exists for toxicity of cadmium to invertebrate species as with fish, the slope from the fish acute equation was used to determine the logarithmic intercepts (relative species sensitivity) for invertebrate species. The intercepts ranged from -1.02 for the scud (Gammarus sp.) to 3.74 for damselfly, with a mean of 1.47. After adjustment using the species sensitivity factor of 21, the intercept is -1.57. This would indicate that the invertebrate species tested are acutely less sensitive to cadmium than fish. Therefore, the Final Fish Acute Value becomes the Final Acute Value.

Chronic Toxicity

The fish chronic values ranged from 0.9 to 50 µg/l (Table 3). Except for the fathead minnow and bluegill which were tested in hard water, all chronic values were in the range of 0.9 to 7.5 µg/l. Consistent with the acute tests, salmonids tended to be the most sensitive group. The three sets of brook trout data by three different investigators may be in closer agreement than indicated (Table 3). Without the use of the embryo-larval adjustment factor of 2 they are practically identical. However, LC10 values (Chapman, In press) as low as 0.7 µg/l (Table 7) were also obtained for rainbow trout. Because of the extent to which Chapman (In press) investigated the sensitivity of various life stages, these results are probably more nearly comparable to embryo-larval test results. The only chronic test data relating fish chronic toxicity to hardness (Sauter, 1976) is unexplainably contradictory. Brook trout were found to be several times more sensitive in soft water than hard water, while channel catfish were equally sensitive in both.

Toxicity and hardness data for brook trout were used to determine the slope for the hardness relationship, since the data available for channel catfish seemed to be inconsistent with the rest of the data on acute and chronic toxicity. Using the book trout slope (0.867), calculated intercepts for the 12 species tested ranged from -2.98 for brook trout to -0.71 for bluegill, with a mean of -1.80. The adjusted mean intercept (-3.70) is below that for all species and is therefore used in the Final Fish Chronic Value.

A chronic value of 0.34 µg/l (Table 4) was obtained for Daphnia magna from the data of Biesinger and Christensen (1972) for reproductive impairment in Daphnia magna. Marshall (1978) found the long-term (22 week) average numbers of Daphnia galeata mendotae in laboratory populations in harder Lake Michigan water (the hardness was estimated to be 120 mg/l) were reduced by 50 percent at 7.7 µg/l (Table 7). A concentration of 4 µg/l and higher significantly reduced biomass.

The three application factors for fish are surprisingly similar considering the different species and water hardness involved. In the case of the one set of comparable invertebrate data, a similar wide difference between acute (65 µg/l) and chronic (0.34 µg/l) test results was observed for Daphnia magna (Biesinger and Christensen, 1972). An invertebrate application factor derived from values (0.00523) would be very similar to those for the fish.

Only a single chronic toxicity test with Daphnia magna is available for cadmium. The chronic value obtained, however, is significantly below that for any fish species at equivalent hardness.

Daphnia magna and other cladocerans are the most sensitive invertebrate species tested (Table 2). Therefore, it would appear to be inappropriate to use the Guidelines species sensitivity factor of 5.1 with the chronic data for *Daphnia magna*. Consequently, that sensitivity factor will not be used in the calculations to derive the Final Invertebrate Chronic Value. Since appropriate invertebrate data were not available to establish a relationship between chronic toxicity values and hardness, a relationship was estimated by using the slope (0.867) from the Final Fish Chronic Value and the cadmium value and water hardness from the *Daphnia magna* test. The calculated intercept for invertebrate species is -4.38. The derived equation for invertebrate species $e^{(0.867 \ln(\text{hardness}) -4.38)}$ becomes the Final Chronic Value since it is lower than the comparable value for fish.

Plant Effects

Growth reduction was the major effect employed for detecting toxicity to aquatic plants (Table 5). Species ranged from diatoms to duckweed. Correspondingly, the effect concentrations ranged from 2 µg/l for the diatom (Conway, 1978) to 7,400 µg/l for Eurasian watermilfoil (Stanley, 1974). Some values were lower than several LC50 values for fish. Although some plant studies demonstrated toxicity at low cadmium concentrations, it must be considered that growth media, used to sustain the plants, appeared to be less similar with respect to components added to natural lake and stream waters than dilution waters used in fish toxicity test. Since toxicity values for fish and invertebrate species were lower than plant data, these data do not enter into formulation of the criterion.

Residues

Bioconcentration factors (Table 6) ranged from 151 for brook trout (Benoit, et al. 1976) to 1,988 for flagfish (Spehar, 1976). By comparison, brook trout was observed to approach steady-state bioconcentration much more slowly (Benoit, et al. 1976) than *Daphnia magna* (Poldoski, manuscript). In the work with *Daphnia magna*, the species displaying the lowest chronic value, significant bioconcentration occurred within 1 day. The work of Hutchinson and Czyska (1972) provided the only available values for plants, 603 and 960.

One noteworthy characteristic of cadmium bioconcentration is the possible long half-life of residues. Benoit, et al. (1976) found that certain organs did not lose significant amounts of cadmium when exposed trout were placed in clean water for several weeks.

When the mallard was fed a diet containing 20 mg cadmium/kg for 90 days, there was testicular damage (White, et al. In press). Division of 29 mg/kg by the geometric mean bioconcentration factor of 515 gives a Residue Limited Toxicant Concentration (RLTC) of 39 µg/l.

CRITERION FORMULATION

Freshwater - Aquatic Life

Summary of Available Data

Final Fish Acute Value = $e^{(1.30\ \ln(\text{hardness})-3.92)}$

Final Invertebrate Acute Value = $e^{(1.30\ \ln(\text{hardness})-1.57}$

Final Acute Value = $e^{(1.30\ (\text{hardness})-3.92}$

Final Fish Chronic Value = $e^{(0.867\ \ln(\text{hardness})-3.70)}$

Final Invertebrate Chronic Value = $e^{(0.867\ \ln(\text{hardness})-4.38)}$

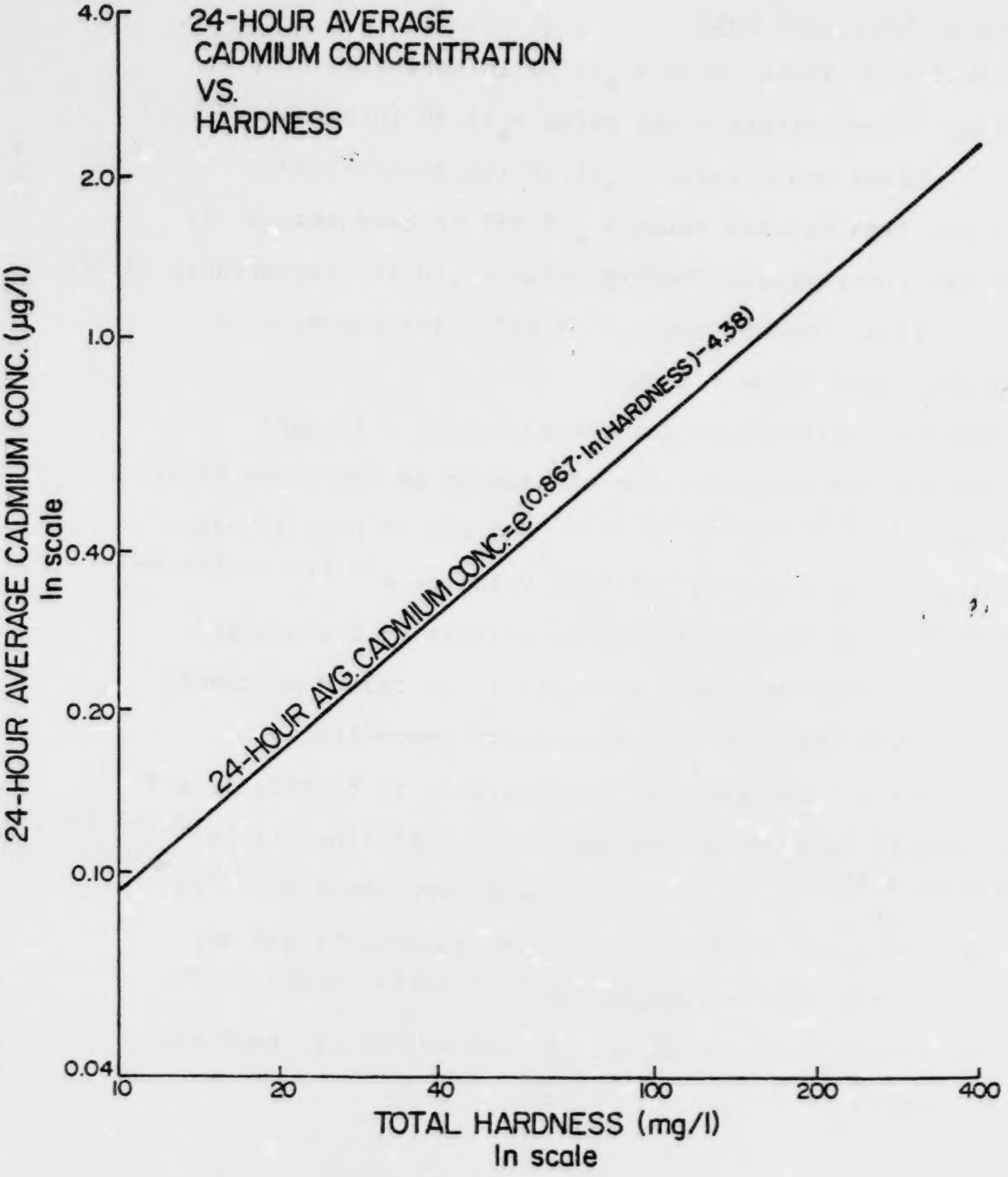
Final Chronic Value = (0.867 ln(hardness)-4.38)

Final Plant Value = 2 µg/l

Residue Limited Toxicant Concentration = 39 µg/l

The maximum concentration of cadmium is the Final Acute Value of $e^{(1.30\ \ln(\text{hardness})-3.92)}$ and the 24-hour average concentration is the Final Chronic Value of $e^{(0.867\ \ln\text{-}(\text{hardness})-4.38)}$. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For cadmium the criterion to protect freshwater aquatic life as derived using the Guidelines is "$e^{(0.867\ \ln\text{-}(\text{hardness})-4.38)}$" as a 24-hour average (see the figure "24-hour average cadmium concentration vs. hardness") and the concentration should not exceed "$e^{(1.30\ \ln(\text{hardness})-3.92)}$" (see the figure "maximum cadmium concentration vs. hardness") at any time.


24-HOUR AVERAGE
CADMIUM CONCENTRATION
VS.
HARDNESS
24-HOUR AVG. CADMIUM CONC.=$e^{(0.867 \cdot \ln(\text{HARDNESS}) - 4.38)}$
24-HOUR AVERAGE CADMIUM CONC. (μg/l)
ln scale
4.0
2.0
1.0
0.40
0.20
0.10
0.04
10
20
40
100
200
400
TOTAL HARDNESS (mg/l)
ln scale

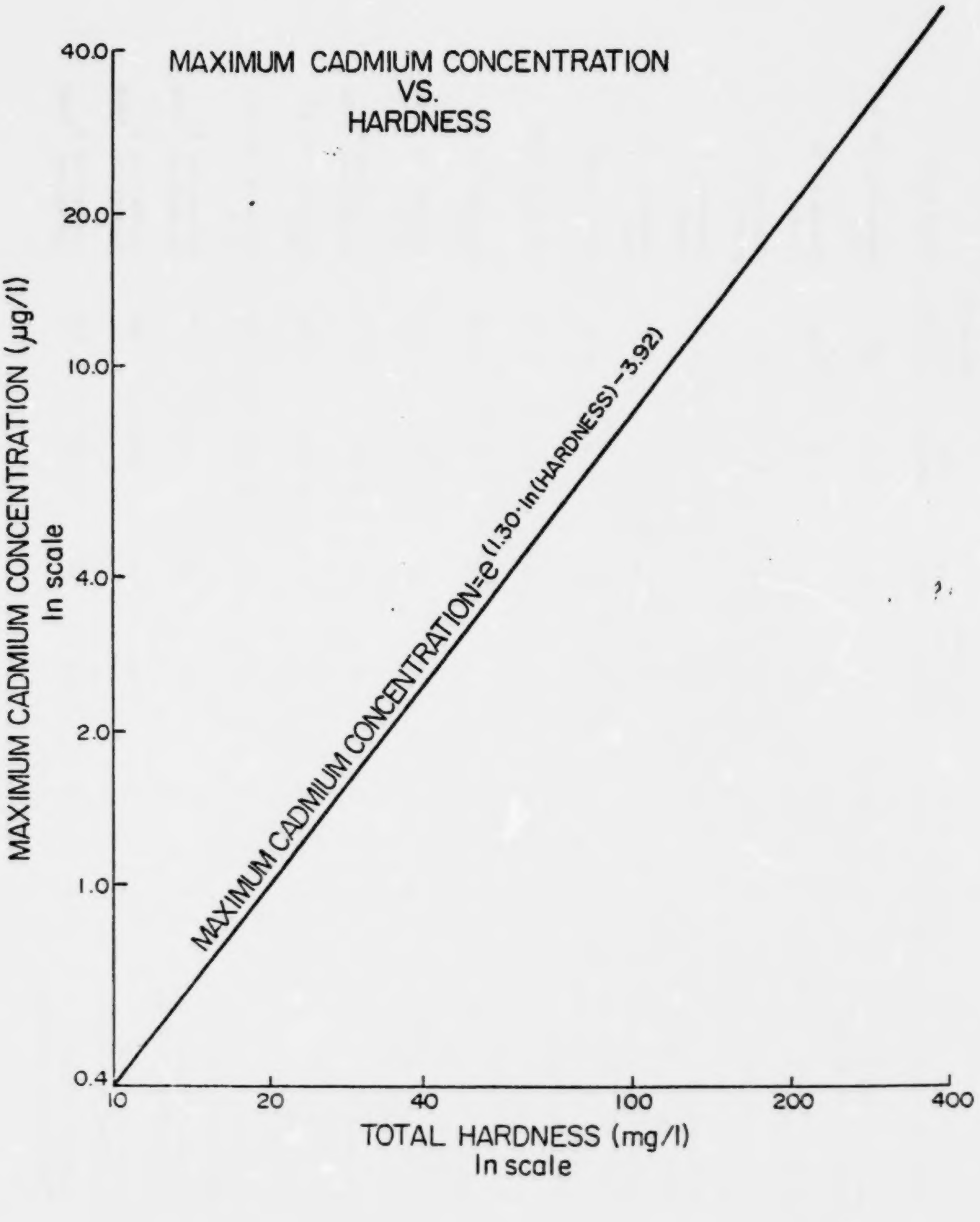

MAXIMUM CADMIUM CONCENTRATION
VS.
HARDNESS
MAXIMUM CADMIUM CONCENTRATION (µg/l)
ln scale
40.0
20.0
10.0
4.0
2.0
1.0
0.4
10
20
40
100
200
400
TOTAL HARDNESS (mg/l)
ln scale
MAXIMUM CADMIUM CONCENTRATION=e (1.30·ln(HARDNESS)−3.92)

Table 1. Freshwater fish acute values for cadmium

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
American eel, *Anguilla rostrata*	S	M	55	96	820	582	Rehwoldt, et al. 1972
Chinook salmon (swim-up), *Oncorhynchus tshawytscha*	FT	M	23	96	1.8	1.8	Chapman, In press
Chinook salmon (parr), *Oncorhynchus tshawytscha*	FT	M	23	96	3.5	3.5	Chapman, In press
Rainbow trout (swim-up), *Salmo gairdneri*	FT	M	23	96	1.3	1.3	Chapman, In press
Rainbow trout (parr), *Salmo gairdneri*	FT	M	23	96	1.0	1.0	Chapman, In press
Rainbow trout (2-mos), *Salmo gairdneri*	FT	M	--	96	6.6	6.6	Hale, 1977
Rainbow trout, *Salmo gairdneri*	FT	M	31	96	1.75	1.75	Davies, 1976
Rainbow trout, *Salmo gairdneri*	S	U	--	96	6	3.28	Kumada, et al. 1973
Rainbow trout, *Salmo gairdneri*	S	U	--	96	7	3.83	Kumada, et al. 1973
Goldfish, *Carassius auratus*	S	U	20	96	2,340	1,279	Pickering & Henderson, 1966
Goldfish, *Carassius auratus*	S	M	20	96	2,130	1,512	McCarty, et al. 1978
Goldfish, *Carassius auratus*	S	M	140	96	46,800	33,228	McCarty, et al. 1978
Fathead minnow, *Pimephales promelas*	S	U	20	96	1,050	574	Pickering & Henderson, 1966
Fathead minnow, *Pimephales promelas*	S	U	20	96	630	344	Pickering & Henderson, 1966
Fathead minnow, *Pimephales promelas*	S	U	360	96	72,600	39,690	Pickering & Henderson, 1966

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)	Reference
Fathead minnow, *Pimephales promelas*	S	U	360	96	73,500	40,182	Pickering & Henderson, 1966
Fathead minnow, *Pimephales promelas*	FT	M	201	96	11,000	11,000	Pickering & Gast, 1972
Fathead minnow, *Pimephales promelas*	FT	M	201	96	12,000	12,000	Pickering & Gast, 1972
Fathead minnow, *Pimephales promelas*	FT	M	201	96	6,400	6,400	Pickering & Gast, 1972
Fathead minnow, *Pimephales promelas*	FT	M	201	96	2,000	2,000	Pickering & Gast, 1972
Fathead minnow, *Pimephales promelas*	FT	M	201	96	4,500	4,500	Pickering & Gast, 1972
Carp, *Cyprinus carpio*	S	M	55	96	240	170	Rehwoldt, et al. 1972
Banded killifish, *Fundulus diaphanus*	S	M	55	96	110	78	Rehwoldt, et al. 1972
Flagfish, *Jordanella floridae*	FT	M	44	96	2,500	2,500	Spehar, 1976
Mosquitofish, *Gambusia affinis*	FT	M	10.0	96	1,300	1,300	Giesy, et al. 1977
Mosquitofish, *Gambusia affinis*	FT	M	10.0	96	1,400	1,400	Giesy, et al. 1977
Mosquitofish, *Gambusia affinis*	FT	M	10.0	96	2,600	2,600	Giesy, et al. 1977
Mosquitofish, *Gambusia affinis*	FT	M	11.1	96	900	900	Giesy, et al. 1977
Mosquitofish, *Gambusia affinis*	FT	M	11.1	96	2,200	2,200	Giesy, et al. 1977
Guppy, *Lebistes reticulatus*	S	U	20	96	1,270	694	Pickering & Henderson, 1966

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Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)	Reference
Threespine stickleback, *Gastrosteys aculeatus*	S	U	115	96	6,500	3,554	Pascoe & Cram, 1977
Threespine stickleback, *Gastrosteys aculeatus*	R	M	103-111	96	23,000	16,330	Pascoe & Mattey, 1977
Striped bass, *Roccus saxatilus*	S	M	55	96	1,100	781	Rehwoldt, et al. 1972
Striped bass (larva), *Roccus saxatilus*	S	U	70	96	1	0.55	Hughes, 1973
Striped bass (fingerling), *Roccus saxatilus*	S	U	70	96	2	1.09	Hughes, 1973
Green sunfish, *Lepomis cyanellus*	S	U	20	96	2,840	1,553	Pickering & Henderson, 1960
Green sunfish, *Lepomis cyanellus*	S	U	360	96	66,000	36,082	Pickering & Henderson, 1960
Green sunfish, *Lepomis cyanellus*	FT	M	335	96	20,500	20,500	Jude, 1973
Pumpkinseed, *Lepomis gibbosus*	S	M	55	96	1,500	1,065	Rehwoldt, et al. 1972
Bluegill, *Lepomis macrochirus*	S	U	20	96	1,940	1,061	Pickering & Henderson, 1960
Bluegill, *Lepomis macrochirus*	FT	M	207	96	21,100	21,100	Andrew, et al. Manuscript
White perch, *Roccus americanus*	S	M	55	96	8,400	5,964	Rehwoldt, et al. 1972

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* S = static, FT = flow-through, R = renewal

** U = unmeasured, M = measured

Table 1. (Continued)

Organism	Bioassay Method	Test Conc.	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)	Reference

Adjusted LC50 vs. hardness:

Goldfish: slope = 1.63, intercept = 2.35, r = 0.99, Not significant, N = 3

Fathead minnow: slope = 1.37, intercept = 1.82, r = 0.91, p = 0.01, N = 9

Green sunfish: slope = 1.01, intercept = 4.33, r = 0.99, Not significant, N = 3

Bluegill: slope = 1.28, intercept = 3.13, r = 1.0, Not significant, N = 2

Geometric mean slope = 1.30

Mean intercept for 16 fish species = 1.20

Adjusted mean intercept = 1.20 - ln(3.9) = -0.16

Intercept for rainbow trout = -3.92

Final Fish Acute Value $= e^{(1.30 \cdot \ln(\text{hardness})-3.92)}$

Table 2. Freshwater invertebrate acute values for cadmium

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Rotifer, *Philodina acuticornis*	R	U	25	96	500	424	Buikema, et al. 1974
Rotifer, *Philodina acuticornis*	R	U	25	96	200	169	Buikema, et al. 1974
Rotifer, *Philodina acuticornis*	R	U	81	96	300	254	Buikema, et al. 1974
Bristle worm, *Nais* sp.	S	U	50	96	1,700	1,440	Rehwoldt, et al. 1973
Snail (egg), *Amnicola* sp.	S	U	50	96	3,800	3,219	Rehwoldt, et al. 1973
Snail (adult), *Amnicola* sp.	S	U	50	96	8,400	7,115	Rehwoldt, et al. 1973
Cladoceran, *Daphnia hyalina*	S	U	--	48	55	47	Baudouin & Scoppa, 1974
Cladoceran, *Daphnia magna*	S	U	45	48	65	55	Biesinger & Christensen, 1972
Cladoceran, *Simoephalus serrulatus*	S	M	10.0	48	35.0	38.5	Giesy, et al. 1977
Cladoceran, *Simoephalus serrulatus*	S	M	11.1	48	7.0	7.7	Giesy, et al. 1977
Cladoceran, *Simoephalus serrulatus*	S	M	11.1	48	3.5	3.8	Giesy, et al. 1977
Cladoceran, *Simoephalus serrulatus*	S	M	11.1	48	12.0	13.2	Giesy, et al. 1977
Cladoceran, *Simoephalus serrulatus*	S	M	11.1	48	16.5	18.1	Giesy, et al. 1977
Cladoceran, *Simoephalus serrulatus*	S	M	11.1	48	8.6	9.5	Giesy, et al. 1977
Copepod, *Cyclops abyssorum*	S	U	--	48	3,200	1,384	Baudouin & Scoppa, 1974

Table 2. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)	Reference
Copepod, *Eudiaptomus padanus*	S	U	--	48	550	200	Baudouin & Scoppa, 1974
Scud, *Gammarus sp.*	S	U	50	96	70	59	Rehwoldt, et al. 1973
Mayfly, *Ephemerella grandis grandis*	FT	M	--	96	28,000	28,000	Clubb, et al. 1975
Mayfly, *Ephemerella grandis grandis*	S	M	54	96	2,000	2,200	Warnick & Bell, 1969
Stonefly, *Pteronarcella bodia*	FT	M	--	96	18,000	18,000	Clubb, et al. 1975
Damselfly, Unidentified	S	U	50	96	8,100	6,861	Rehwoldt, et al. 1973
Midge, *Chironomous*	S	U	50	96	1,200	1,016	Rehwoldt, et al. 1973
Caddisfly, Unidentified	S	U	50	96	3,400	2,880	Rehwoldt, et al. 1973

* S = static, FT = flow-through, R = renewal

** U = unmeasured, M = measured

Adjusted LC50 vs. hardness:

No hardness relationship could be derived for any invertebrate species.

Using the geometric mean slope from the fish acute values, the mean intercept for 10 invertebrate species = 1.47

Adjusted mean intercept = 1.47 - ln(21) = -1.57

Final Invertebrate Acute Value $= e^{(1.30 \cdot \ln(\text{hardness}) - 1.57)}$

Table 3. Freshwater fish chronic values for cadmium

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)	Hardness (mg/l as $CaCO_3$)	Reference
Coho salmon (Lake Superior), *Oncorhynchus kisutch*	E-L	1.3-3.4	1.0	44	Eaton, et al. 1978
Coho salmon (West Coast), *Oncorhynchus kisutch*	E-L	4.1-12.5	3.6	44	Eaton, et al. 1978
Brook trout, *Salvelinus fontinalis*	E-L	1.1-3.8	1.0	44	Eaton, et al. 1978
Brook trout, *Salvelinus fontinalis*	LC	1.7-3.4	2.4	44	Benoit, et al. 1976
Brook trout, *Salvelinus fontinalis*	E-L	1-3	0.9	36	Sauter, et al. 1976
Brook trout, *Salvelinus fontinalis*	E-L	7-12	4.6	187	Sauter, et al. 1976
Lake trout, *Salvelinus namaycush*	E-L	4.4-12.3	3.7	44	Eaton, et al. 1978
Brown trout, *Salmo trutta*	E-L	3.8-11.7	3.3	44	Eaton, et al. 1978
Northern pike, *Esox lucius*	E-L	4.2-12.9	3.7	44	Eaton, et al. 1978
Fathead minnow, *Pimephales promelas*	LC	37-57	46	201	Pickering & Gast, 1972
White sucker, *Catostomus commersoni*	E-L	4.2-12.0	3.5	44	Eaton, et al. 1978
Channel catfish, *Ictalurus punctatus*	E-L	11-17	6.8	37	Sauter, et al. 1976
Channel catfish, *Ictalurus punctatus*	E-L	12-17	7.1	185	Sauter, et al. 1976
Flagfish, *Jordanella floridae*	LC	4.1-8.1	5.8	44	Spehar, 1976
Smallmouth bass, *Micropterus dolomieui*	E-L	4.3-12.7	3.7	44	Eaton, et al. 1978

Table 3. (Continued)

Organism	Test*	Limits (µg/l)	Chronic Value (µg/l)	Hardness (mg/l as $CaCO_3$)	Reference
Bluegill, *Lepomis macrochirus*	LC	31-80	50	207	Eaton, 1974
Walleye, *Stizostedion vitreum*	E-L	9-25	7.5	35	Sauter, et al. 1976

* E-L = embryo-larval, LC= life cycle or partial life cycle

Fish chronic value vs. hardness:

Brook trout: slope = 0.867, intercept = -2.98, r = 0.86, Not significant, N = 4

Geometric mean slope = 0.867 (only value available)

Mean intercept for 12 fish species = -1.80

Adjusted mean intercept = -1.80-ln(6.7) = -3.70

Final Fish Chronic Value = $e^{(0.867 \cdot \ln(\text{hardness}) - 3.70)}$

Application Factor Values**

Species	96-hr LC50 (µg/l)	MATC (µg/l)	AF	Reference
Fathead minnow, *Pimephales promelas*	5,973	37-57	0.00770	Pickering & Gast, 1972
Flagfish, *Jordanella floridae*	2,500	4.1-8.1	0.00232	Spehar, 1976
Bluegill, *Lepomis macrochirus*	21,100	31-80	0.00237	Andrew, et al. Manuscript

Geometric mean AF = 0.00348

** The Final Fish Chronic Value is below the chronic value derived using the application factor.

Table 4. Freshwater invertebrate chronic values for cadmium (Biesinger & Christensen, 1972)

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)	Hardness (mg/l as $CaCO_3$)
Cladoceran, *Daphnia magna*	LC	0.17-0.7	0.34**	45

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* LC = life cycle or partial life cycle

** Hardness = 45 mg/l as $CaCO_3$

Invertebrate chronic value vs. hardness:

No hardness relationship could be derived for any invertebrate species.

Slope = 0.867 from fish chronic values

Intercept for *Daphnia* = -4.38 (only species tested)

Final Invertebrate Chronic Value = $e^{(0.867 \cdot \ln(\text{hardness}) - 4.38)}$

Table 5. Freshwater plant effects for cadmium

Organism	Effect	Concentration (µg/l)	Reference
Diatom, *Asterionella formosa*	Factor of 10 growth rate decrease	2	Conway, 1978
Diatom, *Scenedesmus quadracauda*	Reduction in cell count	6.1	Klass, et al. 1974
Green alga, *Chlorella pyrenoidosa*	Reduction in growth	250	Hart & Scaife, 1977
Green alga, *Chlorella vulgaris*	Reduction in growth	50	Hutchinson & Stokes, 1975
Green alga, *Chlorella vulgaris*	50% reduction in growth	60	Rosko & Rachlin, 1977
Green alga, *Selanastrum capricornutum*	Reduction in growth	50	Bartlett, et al. 1974
Fern, *Salvina natans*	Reduction in number of fronds	10	Hutchinson & Czyrska, 1972
Eurasian watermilfoil, *Myriophyllum spicatum*	50% root weight inhibition	7,400	Stanley, 1974
Duckweed, *Lemna valdiviana*	Reduction in number of fronds	10	Hutchinson & Czyrska, 1972

Lowest plant value = 2 µg/l

Table 6. Freshwater residues for cadmium

Organism	Bioconcentration Factor	Time (days)	Reference
Duckweed, *Lemna valdiviana*	603	21	Hutchinson & Czyrska, 1972
Fern, *Salvinia natans*	960	21	Hutchinson & Czyrska, 1972
Cladoceran, *Daphnia magna*	320	2-4	Poldoski, Manuscript
Crayfish, *Orconectes propinquus*	184	8	Gillespie, et al. 1977
Rainbow trout, *Salmo gairdneri*	540	140	Kumada, et al. 1973
Brook trout, *Salvelinus fontinalis*	3*	490	Benoit, et al. 1976
Brook trout, *Salvelinus fontinalis*	151	84	Benoit, et al. 1976
Flagfish, *Jordanella floridae*	1,988	30	Spehar, 1976
Threespined stickleback, *Gastrosteus aculeatus* L.	900	33	Pascoe & Mattey, 1977

Maximum Permissible Tissue Concentration

Organism	Action Level or Effect	Concentration (mg/kg)	Reference
Mallard, *Anas platyrhynchos*	Testicular damage, 90 days	20	White, et al. In press

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* Indicates muscle tissue only, data not used in calculating geometric mean bioconcentration factors.

Geometric mean bioconcentration factor for all species = 515

Lowest residue concentration = 20 mg/kg

$\frac{20}{515}$ = 0.039 mg/kg or 39 µg/l

Table 7. Other freshwater data for cadmium

Organism	Test Duration	Effect	Hardness, mg/l ($CaCO_3$)	Result (µg/l)	Reference
Cladoceran, Daphnia galeata mendotae	22 wks	50 percent reduction in relative mean numbers	--*	7.7	Marshall, 1978
Cladoceran, Daphnia galeata mendotae	22 wks	Reduced biomass	--*	4.0	Marshall, 1978
Coho salmon (juvenile), Oncorhynchus kisutch	217 hrs	LC50	22	2.0	Chapman & Stevens, In press
Coho salmon (adult), Oncorhynchus kisutch	215 hrs	LC50	22	3.2	Chapman & Stevens, In press
Chinook salmon (alevin), Oncorhynchus tshawytscha	200 hrs	LC10	23	18-26	Chapman, In press
Chinook salmon (swim-up), Oncorhynchus tshawytscha	200 hrs	LC10	23	1.2	Chapman, In press
Chinook salmon (parr), Oncorhynchus tshawytscha	200 hrs	LC10	23	1.3	Chapman, In press
Chinook salmon (smolt), Oncorhynchus tshawytscha	200 hrs	LC10	23	1.5	Chapman, In press
Brook trout, Salvelinus fontinalis	21 days	Testicular damage (blood vessel collapse, reduced 11-ketotestosterone synthesis	20	10	Sangalang & O'Halloran, 1972, 1973
Rainbow trout, Salmo gairdneri	240 hrs	LC50	--	7	Kumada, et al. 1973
Rainbow trout, Salmo gairdneri	240 hrs	LC50	--	5	Kumada, et al. 1973
Rainbow trout (juvenile), Salmo gairdneri	390 hrs	LC50	--	0.9	Chapman & Stevens, In press
Rainbow trout (adult), Salmo gairdneri	408 hrs	LC50	--	4.8	Chapman & Stevens, In press

Table 7. (Continued)

Organism	Test Duration	Effect	Hardness, mg/l ($CaCO_3$)	Result (ug/l)	Reference
Rainbow trout (alevin), *Salmo gairdneri*	186 hrs	LC10	23	>6	Chapman, In press
Rainbow trout (swim-up), *Salmo gairdneri*	200 hrs	LC10	23	1.0	Chapman, In press
Rainbow trout (parr), *Salmo gairdneri*	200 hrs	LC10	23	0.7	Chapman, In press
Rainbow trout (smolt), *Salmo gairdneri*	200 hrs	LC10	23	0.8	Chapman, In press
Rainbow trout, *Salmo gairdneri*	96 hrs	LC20	326	20	Davies, 1976
Goldfish, *Carassius auratus*	50 days	Reduced plasma sodium level (osmo-rigulatory changes)	--	44.5	McCarty & Houston, 1976
Threespine stickleback, *Gasterosteus aculeatus*	33 days	LC50	--	0.8	Pascoe & Mattey, 1977

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* Tests were conducted in water from Lake Michigan.

SALTWATER ORGANISMS

Acute Toxicity

Data on acute cadmium toxicity to saltwater fishes covers four species, different life stages and exposure conditions (Table 8). Unadjusted LC50 values ranged from 1,600 µg/l for larval Atlantic silversides (Middaugh and Dean, 1977) to 114,000 µg/l for juvenile mummichog (Voyer, 1975). Intraspecific differences in sensitivity relating to life stage are also evident. Middaugh and Dean (1977) have shown that larvae of the mummichog and Atlantic silverside were an average of four times more sensitive than adults tested under the same conditions. Studies of the effect of salinity on cadmium toxicity to adult mummichog and Atlantic silverside indicate cadmium is more toxic at 30 °/oo than at 20 °/oo (Voyer, 1975; Middaugh and Dean, 1977).

When the geometric mean LC50 (11,010 µg/l is divided by the sensitivity factor of 3.7, the result is 3,000 µg/l (Table 8). This concentration becomes the Final Fish Acute Value for saltwater fish and cadmium.

This result is higher than adjusted LC50 values for larvae of the Atlantic silverside. The geometric mean of six tests (Middaugh and Dean, 1977) is 1,800 µg/l. However, the geometric mean LC50 value for combined data for adults and larvae is 3,600 µg/l. In addition, the acute toxicity data base for saltwater fish is limited to four species of which three are in the same family (Cyprinodontidae). The data base is too limited to evaluate the applicability to cadmium of the sensitivity factor.

A variety of saltwater invertebrate species are more sensitive to acute cadmium poisoning than saltwater fishes (Table 9). The invertebrate data include results of studies on four phyla: Annelida, Mollusca, Anthropoda (Crustaceans) and Echinoderms. The adjusted LC50 values ranged from 15.5 µg/l for Mysidopsis bahia (Nimmo, et al. 1977a) to 39,470 µg/l for the fiddler crab (O'Hara, 1973). Adult and juvenile polychaete worms were relatively insensitive to cadmium with adjusted LC50 values ranging from 6,353 to 10,588 µg/l (Reish, et al. 1976). Larvae of the polychaete (Capitella capitata), however, were more sensitive than the adult (Reish, et al. 1976). The gastropod molluscs were also relatively insensitive to cadmium as evidenced by the values for the mud snail, 35,000 µg/l (Eisler and Hennekey, 1977) and the oyster drill, 6,600 µg/l (Eisler, 1972). The unadjusted LC50 values for the bivalve molluscs ranged from 1,480 µg/l for the bay scallop (Nelson, et al. 1976) to 4,300 µg/l for the mussel (Ahsanullah, 1976). The data from Eisler (1971) on the mussel is atypical with a 96-hour LC50 of 25,000 µg/l. The arthropods (Crustaceans) manifested the widest range of sensitivity to acute cadmium exposure. The most sensitive species and their unadjusted LC50 values were: Mysidopsis bahia (15.5 µg/l); Homarus americanus (78 µg/l); and Acartia tonsa (90 µg/l). The least sensitive species was the crab, Uca pugilator with 96-hour LC50 values as high as 46,600 µg/l.

Acute cadmium toxicity to Uca pugilator was not altered by salinities of 10, 20, and 30 °/oo. Temperature, however, increased cadmium toxicity by a factor of five between 20°C and 30°C at 10 °/oo and by a factor of 1.6 at 30 °/oo.

When the geometric mean of 1,550 µg/l is divided by the species sensitivity factor of 49 the result is 32 µg/l (Table 9). The data base, however, contains a flow-through, measured LC50 value of 15.5 µg/l for Mysidopsis bahia. Using the recommended Guideline's procedures of selecting the lower of these two values, the Final Invertebrate Acute Value is 16 µg/l. All the values reported in Table 9 are equal to or greater than 16 µg/l.

Since the Final Invertebrate Acute Value of 16 µg/l is lower than the Final Fish Acute Value of 3,000 µg/l, the Final Acute Value for saltwater aquatic life is 16 µg/l.

Chronic Toxicity

No life cycle or embryo-larval data are available with cadmium for saltwater fishes.

The chronic toxicity of cadmium to the mysid shrimp, Mysidopsis bahia was studied (Table 10). Four parameters were addressed; survival, appearance of first brood, time of release of young from the brood pouch, and the average number of young per female released after a 23-day exposure. Decreased survival (90 percent) was evident at 10.6 g/l; a 48-hour delay in brood formation and 24-hour delay in brood release at 6.4 µg/l was observed and a 57 percent decrease in the number of young per female occurred at 6.4 µg/l. There were no measurable effects on the above parameters at 4.8 µg/l. For Msidopsis bahia, with its short-life cycle, the difference between the 96-hour LC50 and chronic toxicity of cadmium is small (i.e., 15.5 ug/l to 4.8 µg/l). Comparison of acute and chronic mortality data for other invertebrate species indicates a wider range of response. The acute toxicity values for Penaeus duorum (3,500 µg/l), Paleomentes vulgaris (760 µg/l). Capitella capitata (7,500 ug/l), and Neanthes arenaceodentata (12,000 µg/l) are compared to the corresponding 28-day LC50 values (Table 13) of 720 µg/l, 120 µg/l, 700 µg/l, and 3,000 µg/l, respectively. For species with long life cycles, the differences between acute and chronic toxicity are greater than that of the mysid shrimp.

Since chronic toxicity data are limited to one species, no indication of the range of species sensitivity can be determined. Mysidopsis bahia is, however, the most sensitive invertebrate species acutely tested (Table 9). Without additional chronic data, it is difficult to judge the appropriateness of the species sensitivity factor of 5.1 which, when applied to the geometric mean of the chronic value of 5.5 µg/l, results in a Final Invertebrate Chronic Value of 1.0 µg/l. Based upon data on bioconcentration (Table 12) and sublethal effects reported in Table 13, this value is protective of saltwater aquatic life.

Plant Effects

The sensitivity of saltwater plants to cadmium has only been tested with microalgae (Table 11). Cadmium inhibited the growth rate of Skeletonema costatum and Cyclotella nana at 175 µg/l and 160 µg/l, respectively. The Final Plant Value is 160 µg/l.

Bioconcentration

Cadmium is bioconcentrated by a wide variety of marine species (Table 12). The highest bioconcentration factors for cadmium are those with bivalve molluscs. Zaroogian and Cheer (1976) demonstrated that the American oyster could bioconcentrate cadmium 2,600 times after a 280-day exposure. Tissue residues reached 10.75 mg/kg which closely approximate the emetic threshold (13-15 mg/kg) established for man (Anon., 1950). This indicates that a commercially important shellfish can bioconcentrate cadmium to potentially harmful concentrations when the seawater cadmium concentration is only 5 ug/l. Kerfoot and Jacobs (1976) have also shown oyster tissue residues of 16 mg/kg after a 40-day exposure to 30 ug/l. George and Coombs (1977) reported on the effects of metal speciation on accumulation of cadmium in the soft tissues of *Mytilus edulis*. Cadmium complexed as Cd-alginate, Cd-EDTA, Cd-humate, and Cd-pectate was bioconcentrated at twice the rate as $CdCl_2$. Fish bioconcentration factors were 48 for the mummichog (Eisler, 1972). Crustaceans were intermediate between the fish and molluscs in their ability to bioconcentrate cadmium. Vernberg, et al. (1977) reported 700 for grass shrimp while the pink shrimp had a bioconcentration factor of only 57 (Nimmo, et al. 1977b).

A Residue Limited Toxicant Concentration (RLTC) can be derived using the available data base (Table 12). Bioconcentration factors are known for a variety of forms and species from algae to fish. The geometric mean of these factors is 144. When the lowest maximum permissible tissue concentration, 20 mg/kg for the mallard, is divided by 144, the derived RLTC is 140 µg/l.

Miscellaneous

Several studies have reported on the chronic sublethal effects of cadmium on saltwater fish (Table 13). Significant reduction in gill-tissue respiratory rates and alteration of liver enzyme activity have been reported in the cunner after a 30-day exposure to 50 µg/l (MacInnes, et al. 1977). Dawson, et al. (1977) also reported a significant decrease in gill-tissue respiration for striped bass at 0.5 µg/l above ambient after a 30-day but not a 90-day exposure. A similar study on the winter flounder has been reported (Calabrese, et al. 1975). This study demonstrated significant alterations in gill-tissue respiration rates measured *in vitro* after a 60-day exposure to 5 µg/l.

The significance of these sublethal effects on survival, growth, and reproduction have yet to be evaluated. While the above data are not sufficient for development of a criterion, we must be cognizant that there are demonstratable sublethal effects due to chronic exposure at very low cadmium concentrations.

Most of the remaining data in Table 13 are for effects on survival at higher concentrations or for short exposures.

CRITERION FORMULATION

Saltwater - Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures. All concentrations herein are expressed in terms of cadmium.

Final Fish Acute Value = 3,000 μg/l

Final Invertebrate Acute Value = 16 μg/l

Final Acute Value = 16 μg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = 1.0 μg/l

Final Plant Value = 160 μg/l

Residue Limited Toxicant Concentration = 140 μg/l

Final Chronic Value = 1.0 μg/l

0.44 x Final Acute Value = 7.0 μg/l

The maximum concentration of cadmium is the Final Acute Value of 16 μg/l and the 24-hour average concentration is the Final Chronic Value of 1.0 μg/l. No important adverse effects on saltwater organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For cadmium the criterion to protect saltwater aquatic life as derived using the Guidelines is 1.0 μg/l as a 24-hour average and the concentration should not exceed 16 μg/l at any time.

Table 8. Marine fish acute values for cadmium

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Sheepshead minnow, *Cyprinodon variegatus*	S	U	96	50,000	27,335	Eisler, 1971
Mummichog (adult), *Fundulus heteroclitus*	S	M	48	60,000	34,506	Middaugh & Dean, 1977
Mummichog (adult), *Fundulus heteroclitus*	S	M	48	43,000	24,729	Middaugh & Dean, 1977
Mummichog (adult), *Fundulus heteroclitus*	S	U	96	49,000	26,788	Eisler, 1971
Mummichog (adult), *Fundulus heteroclitus*	S	U	96	22,000	12,027	Eisler & Henneky, 1977
Mummichog (juvenile), *Fundulus heteroclitus*	S	U	96	63,000	34,442	Voyer, 1975
Mummichog (juvenile), *Fundulus heteroclitus*	S	U	96	73,000	39,909	Voyer, 1975
Mummichog (juvenile), *Fundulus heteroclitus*	S	U	96	114,000	62,323	Voyer, 1975
Mummichog (juvenile), *Fundulus heteroclitus*	S	U	96	92,000	50,296	Voyer, 1975
Mummichog (juvenile), *Fundulus heteroclitus*	S	U	96	78,000	42,642	Voyer, 1975
Mummichog (juvenile), *Fundulus heteroclitus*	S	U	96	29,000	15,854	Voyer, 1975
Mummichog (juvenile), *Fundulus heteroclitus*	S	U	96	31,000	16,948	Voyer, 1975
Mummichog (juvenile), *Fundulus heteroclitus*	S	U	96	30,000	16,401	Voyer, 1975
Mummichog (larva), *Fundulus heteroclitus*	S	M	48	16,200	9,317	Middaugh & Dean, 1977
Mummichog (larva), *Fundulus heteroclitus*	S	M	48	9,000	5,176	Middaugh & Dean, 1977

Table 8. (Continued)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Mummichog (larva), *Fundulus heteroclitus*	S	M	48	32,000	18,403	Middaugh & Dean, 1977
Mummichog (larva), *Fundulus heteroclitus*	S	M	48	23,000	13,227	Middaugh & Dean, 1977
Mummichog (larva), *Fundulus heteroclitus*	S	M	48	12,000	6,901	Middaugh & Dean, 1977
Mummichog (larva), *Fundulus heteroclitus*	S	M	48	7,800	4,486	Middaugh & Dean, 1977
Striped killifish (adult), *Fundulus majalis*	S	U	96	21,000	11,480	Eisler, 1971
Atlantic silverside (adult), *Menidia menidia*	S	M	48	12,000	6,901	Middaugh & Dean, 1977
Atlantic silverside (adult), *Menidia menidia*	S	M	48	13,000	7,476	Middaugh & Dean, 1977
Atlantic silverside (larva), *Menidia menidia*	S	M	48	3,800	2,185	Middaugh & Dean, 1977
Atlantic silverside (larva), *Menidia menidia*	S	M	48	3,200	1,840	Middaugh & Dean, 1977
Atlantic silverside (larva), *Menidia menidia*	S	M	48	3,400	1,955	Middaugh & Dean, 1977
Atlantic silverside (larva), *Menidia menidia*	S	M	48	2,200	1,265	Middaugh & Dean, 1977
Atlantic silverside (larva), *Menidia menidia*	S	M	48	1,600	920	Middaugh & Dean, 1977

Table 8. (Continued)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)	Reference
Atlantic silverside (larva), *Menidia menidia*	S	M	48	5,600	3,221	Middaugh & Dean, 1977

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* S = static

** U = unmeasured, M = measured

Geometric mean of adjusted values = 11,010 µg/l $\frac{11,010}{3.7}$ = 3,000 µg/l

Table 9. Marine invertebrate acute values for cadmium

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Polychaete worm (adult), *Capitella capitata*	S	U	96	7,500	6,353	Reish, et al. 1976
Polychaete worm (larva), *Capitella capitata*	S	U	96	220	186	Reish, et al. 1976
Polychaete worm (adult), *Neanthes arenaceodentata*	S	U	96	12,000	10,164	Reish, et al. 1976
Polychaete worm (juvenile), *Neanthes arenaceodentata*	S	U	96	12,500	10,588	Reish, et al. 1976
Polychaete worm, *Nereis virens*	S	U	96	9,300	7,877	Eisler & Henneky, 1977
Polychaete worm, *Nereis virens*	S	U	96	11,000	9,317	Eisler, 1971
Bay scallop (juvenile), *Argopecten irradians*	S	U	96	1,480	1,254	Nelson, et al. 1976
American oyster (larva), *Crassostrea virginica*	S	U	48	3,800	3,219	Calabrese, et al. 1973
Soft shelled clam, *Mya arenaria*	S	U	96	2,500	2,118	Eisler & Henneky, 1977
Soft shelled clam, *Mya arenaria*	S	U	96	2,200	1,863	Eisler, 1971
Mussel, *Mytilus edulis*	S	U	96	25,000	21,175	Eisler, 1971
Mussel, *Mytilus edulis planulatus*	S	M	96	1,620	1,782	Ahsanullah, 1976
Mussel, *Mytilus edulis planulatus*	FT	M	96	3,600	3,600	Ahsunullah, 1976
Mussel, *Mytilus edulis planulatus*	FT	M	96	4,300	4,300	Ahsanullah, 1976
Mud snail, *Nassarius obsoletus*	S	U	96	35,000	29,645	Eisler & Henneky, 1977

Table 9. (Continued)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Mud snail, Nassarius obsoletus	S	U	96	10,500	8,894	Eisler, 1971
Oyster drill, Urosalpinx cinerea	S	U	96	6,600	5,590	Eisler, 1971
Calanoid copepod, Acartia tonsa	S	U	96	90	76	Sosnowski & Gentile, 1978
Calanoid copepod, Acartia tonsa	S	U	96	337	285	Sosnowski & Gentile, 1978
Calanoid copepod, Acartia tonsa	S	U	96	220	186	Sosnowski & Gentile, 1978
Calanoid copepod, Acartia tonsa	S	U	96	122	103	Sosnowski & Gentile, 1978
Copepod, Tigriopus japonicus	S	U	72	4,400	2,273	D'Agostino & Finney, 1974
Mysid shrimp, Mysidopsis bahia	FT	M	96	15.5	15.5	Nimmo, et al. 1977a
Green crab, Carcinus maenas	S	U	96	4,100	3,473	Eisler, 1971
Sand shrimp, Crangon septemspinosa	S	U	96	320	271	Eisler, 1971
Mud crab, Eurypanopus depressus	S	U	72	4,900	2,532	Collier, et al. 1973
American lobster (larva), Homarus americanus	S	U	96	78	66	Johnson & Gentile, 1978
Hermit crab, Pagurus longicarpus	S	U	96	320	271	Eisler, 1971
Hermit crab, Pagurus longicarpus	S	U	96	1,300	1,101	Eisler & Henneky, 1977
Grass shrimp, Palaemonetes vulgaris	S	U	96	420	356	Eisler, 1971

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Table 9. (Continued)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Grass shrimp, *Palaemonetes vulgaris*	FT	M	96	760	760	Nimmo, et al. 1977b
Pink shrimp, *Penaeus duorarum*	FT	M	96	3,500	3,500	Nimmo, et al. 1977b
Fiddler crab, *Uca pugilator*	S	U	96	32,200	27,273	O'Hara, 1973
Fiddler crab, *Uca pugilator*	S	U	96	46,600	39,470	O'Hara, 1973
Fiddler crab, *Uca pugilator*	S	U	96	37,000	31,339	O'Hara, 1973
Fiddler crab, *Uca pugilator*	S	U	96	6,800	5,760	O'Hara, 1973
Fiddler crab, *Uca pugilator*	S	U	96	10,400	8,809	O'Hara, 1973
Fiddler crab, *Uca pugilator*	S	U	96	23,300	19,735	O'Hara, 1973
Starfish, *Asterias forbesi*	S	U	96	820	695	Eisler, 1971
Starfish, *Asterias forbesi*	S	U	96	7,100	6,014	Eisler & Henneky, 1977

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* S - static, FT = flow-through

** U = unmeasured, M = measured

Geometric mean of adjusted values = 1,550 µg/l $\frac{1,550}{49} = 32$ µg/l

Lowest value from a flow-through test with measured concentrations = 15.5 µg/l

Table 10. Marine invertebrate chronic values for cadmium (Nimmo, et al. 1977a)

Organism	Test*	Limits (µg/l)	Chronic Value (µg/l)
Mysid shrimp, *Mysidopsis bahia*	LC	4.8-6.4	5.5

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* LC = life cycle or partial life cycle

Geometric mean of chronic values = 5.5 µg/l $\frac{5.5}{5.1} = 1.0$ µg/l

Lowest chronic value = 5.5 µg/l

Table 11. Marine plant effects for cadmium (Gentile & Johnson, 1974)

Organism	Effect	Concentration (µg/l)
Alga, *Cyclotella nana*	96-hr EC-50 growth rate	160
Alga, *Skeletonema costatum*	96-hr EC-50 growth rate	175

Lowest plant value = 160 µg/l

Table 12. Marine residues for cadmium

Organism	Bioconcentration Factor	Time (days)	Reference
American oyster, *Crassostrea virginica*	2,600	280	Zaroogian & Cheer, 1976
American oyster, *Crassostrea virginica*	677	40	Kerfoot & Jacobs, 1976
American oyster, *Crassostrea virginica*	149	21	Eisler, et al. 1972
American oyster, *Crassostrea virginica*	1,230	140	Shuster & Pringle, 1969
Soft shell clam, *Mya arenaria*	160	70	Pringle, et al. 1968
Mussel, *Mytilus edulis*	45*	20	George & Coombs, 1977
Quahaug, *Mercenaria mercenaria*	109	40	Kerfoot & Jacobs, 1976
Bay scallop, *Aquipecten irradians*	168	21	Eisler, et al. 1972
Mummichog, *Fundulus heteroclitus*	48	21	Eisler, et al. 1972
Alga, *Prasinocladus tricornutum*	670*	5	Kerfoot & Jacobs, 1976
Grass shrimp, *Palaemonetes pugio*	700	21	Vernberg, et al. 1977
Shrimp, *Crangon crangon*	37*	40	Dethlefsen, 1977
Pink shrimp, *Penaeus duorarum*	57	30	Nimmo, et al. 1977b
Shore crab, *Carcinus maenas*	120	14	Wright, 1977

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Table 12. (Continued)

Maximum Permissible Tissue Concentration

Organism	Effect	Concentration (mg/kg)	Reference
Mallard, *Anas platyrhynchos*	Testicular damage, 90 days	20	White, et al. In press

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* Dry weight to wet weight conversion

Geometric mean bioconcentration factor for all species = 144

Lowest residue concentration = 20 mg/kg $\frac{20}{144}$ = 0.14 mg/kg or 140 µg/l

Table 13. Other marine data for cadmium

Organism	Test Duration (days)	Effect	Result (ug/l)	Reference
Grass shrimp, Palaemonetes pugio	14	25% mortality	50	Vernberg, et al. 1977
Pink shrimp, Penaeus duorarum	30	50% mortality	720	Nimmo, et al. 1977b
Fiddler crab (adult), Uca pugilator	10	50% mortality	2,900	O'Hara, 1973
Fiddler crab (larva), Uca pugilator	--	Respiratory and activity	1.0	Vernberg, et al. 1974
Hermit crab, Pagurus longicarpus	7	25% mortality	270	Eisler & Henneky, 1977
Rock crab, Cancer irroratus	4	Enzyme activity	1,000	Gould, et al. 1976
Starfish, Asterias forbesi	7	25% mortality	270	Eisler & Henneky, 1977
Sea urchin (embryo), Acanthocidaris crassispina	--	Effect on fertilization	1,600	Kobayashi, 1971
Winter flounder, Pseudopleuronectes americanus	8	Viable hatch-50%	300	Voyer, et al. 1977
Winter flounder, Pseudopleuronectes americanus	60	Increased gill tissue respiration	5	Calabrese, et al. 1975
Spot (larva), Leiostomus xanthurus	9	Incipient LC50	200	Middaugh, et al. 1975
Striped bass (juvenile), Morone saxatilis	90	Significant decrease in enzyme activity	5	Dawson, et al. 1977
Striped bass (juvenile), Morone saxatilis	30	Significant decrease in oxygen consumption	0.5-5.0	Dawson, et al. 1977
Juvenile mullet, Aldrichetta forsteri	5	50% mortality	14,300	Negilski, 1976

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Table 13 (cont.))

Organism	Test Duration (days)	Effect	Result (µg/l)	Reference
Small mouth hardy head, *Atherinasoma microstoma*	7	50% mortality	12,700	Negilski, 1976
Cunner (adult), *Tautogolabrus adspersus*	60	37.5% mortality	100	MacInnes, et al. 1976
Cunner (adult), *Tautogolabrus adspersus*	30	Depressed gill tissue oxygen consumption	50	MacInnes, et al. 1976
Cunner (adult), *Tautogolabrus adspersus*	4	Decreased enzyme activity	3,000	Gould & Karolus, 1974
Colonial hydroid, *Campanularia flexuosa*	--	Enzyme inhibition	40-75	Moore & Stebbing, 1976
Colonial hydroid, *Campanularia flexuosa*	11	Growth rate inhibition	110-280	Stebbing, 1976
Polychaete worm, *Capitella capitata*	28	50% mortality	700	Reish, et al. 1976
Polychaete worm, *Eudistylia vancouveri*	--	Enzyme inhibition	300	May & Brown, 1973
Polychaete worm, *Neanthes arenaceodentata*	28	50% mortality	3,000	Reish, et al. 1976
Polychaete worm, *Neanthes vaali*	7	50% mortality	6,400	Ahsanullah, 1976
Polychaete worm, *Ophryotrocha labronica*	17	50% mortality	1,000	Brown & Ahsanullah, 1971
Cockle, *Cardium edule*	4	50% mortality	2,000	Portmann & Wilson, 1971
Soft shell clam, *Mya arenaria*	7	50% mortality	700	Eisler & Henneky, 1977
Copepod, *Tigriopus japonicus*	3	Inhibition-egg development	40	D'Agostino & Finney, 1974
Opossum shrimp, *Mysidopsis bahia*	17	50% mortality	11.3	Nimmo, et al. 1977a

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Table 13 (cont.)

Organism	Test Duration	Effect	Result (µg/l)	Reference
Amphipod, *Allorchestes compressa*	5	50% mortality	200-400	Ahsanullah, 1976
Isopod, *Idotea baltica*	5	50% mortality	10,000	Jones, 1975
Grass shrimp, *Palaemonetes vulgaris*	29	50% mortality	120	Nimmo, et al. 1977b

CADMIUM

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Mammalian Toxicology and Human Health Effects

Introduction

Over 50 years have now passed since the first fatal case of acute industrial cadmium poisoning was reported (Legge, 1924) by the British Factory Inspectorate. During the ensuing decades attention was primarily paid to further cases of acute cadmium poisoning occuring via inhalation in industry or through ingestion (Frant and Kleeman, 1941). Harriet Hardy (Hardy and Skinner, 1947) was among the first to suggest significant chronic effects when she reported five cases of ill health in cadmium exposed workmen who had symptoms of anemia and respiratory complaints. The first definitive reports of chronic effects were those of Friberg (Friberg, 1948a and 1948b) who clearly identified emphysema and renal damage among male workers exposed to cadmium oxide dust in a Swedish alkaline battery factory. That cadmium might be associated with health effects as a result of general environmental pollution was gradually recognized during the 1960's as various investigators examined facets of the endemic disease complex called Itai-Itai in Toyama Prefecture, Japan (Friberg, et al. 1974). These and other reports have spawned a vast literature which now defies concise summarization. Nonetheless, a significant number of excellent general reviews have appeared in recent years and serve as guides to the more significant papers in the scientific literature (Friberg, et al. 1974; Flick, et al. 1971; Kendrey and Roe, 1969; Nordberg, 1974; Fleischer, et al. 1974; Buell, 1975; Perry, et al. 1976; Fassett, 1975; Webb, 1975; U.S. EPA, 1975b, 1975a.)

EXPOSURE

The major non-occupational routes of human cadmium exposure are through food and tobacco smoke. Data published by the Food and Drug Administration (Compliance Program Evaluation, 1974) based on market basket surveys over 7 years, show that the average cadmium intake of 15 to 20-year-old males is 39 μg/day, which includes that found in water. If this figure is adjusted by the recommended daily calorie intake for various age groups, the average daily cadmium intake from birth to age 50 is 33 μg/d for men and 26 μg/d for women. More recent domestic data based on fecal excretion give intake figures of 18 μg/d and 21 μg/d for teen-age males residing in Dallas, Texas, (Kjellstrom, 1978c) and Chicago, Illinois (Pahren and Kowal, 1978), respectively. The data in Table 1 indicate that the daily intake of cadmium via food for individuals living in the United States is comparable to that in other parts of the world.

TABLE I

Daily Cadmium Intake Via Food

Country	ug/day	Reference
United States	39	Compliance Program Evaluation 1974
Canada	52	Kirkpatrick and Coffin, 1977
West Germany	48	U.S. EPA, 1975b
Rumania	38-64	U.S. EPA, 1975b
Czechoslovakia	60	U.S. EPA, 1975b
Japan (unpolluted area)	59	U.S. EPA, 1975b
Sweden	17	Kjellstrom, 1978a
Australia	30-50	Miller, et al. 1976
New Zealand	21-27	Guthrie and Robinson, 1977

Cadmium is concentrated by certain food crop classes to an appreciable extent. In particular, potatoes, root crops, and leafy vegetables show the greatest tendency in this regard and their cadmium content depends to a high degree on the soil solution concentration of the element (Pahren, et. al. 1978). Municipal sewage sludges, containing high levels of cadmium of industrial origin, applied to agricultural lands as fertilizer are potentially important sources of cadmium entry into the human food chain (Counc. Agric. Sci. Tech. 1976). To date there have been no occurrences of cadmium toxicity in animals or man attributed solely to direct consumption of vegetation grown on land amended with municipal sludge (Garrigan, 1977). The widespread usage of phosphate fertilizers, most of which contain significant amounts of cadmium (U.S. EPA, 1975a), is potentially a more important source of cadmium entry into human foodstuffs and will ultimately increase the amount of cadmium in the diet.

Balanced diets generally contain approximately 0.05 mg/Kg of cadmium (Nordberg, 1974). Aquatic food species including fish, crabs, oysters, and shrimps bioconcentrate cadmium, as do visceral meats (liver, kidney, pancreas). Cadmium content depends on the age of animals at slaughter, older animals having higher concentrations (Kreuzer, et al. 1976; Nordberg, 1974).

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms. Since BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States, some have to be estimated. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the 19 major species identified in the survey, the relative consumption of the four major groups can be calculated.

Benoit, et al. (1976) found a BCF of three for cadmium in muscle of brook trout. All other tests with freshwater and saltwater fish reported data for the whole body or for non-edible tissues that accumulated more cadmium than muscle. Since no data are available for saltwater fish, they will be assumed to be comparable to freshwater fish. Many studies have been conducted with saltwater molluscs (Zaroogian and Cheer, 1976; Kerfoot and Jacobs, 1976; Eisler, et al. 1972; Schuster and Pringle, 1969; Pringle, et al. 1968; and George and Combs, 1977) with values ranging from 45 to 2,600. A geometric mean was calculated to be 158. Eisler, et al. (1972) found a BCF of 5 for lobster muscle after correcting for lead in the muscle of the control organisms.

Group	Consumption (Percent)	Bioconcentration factor
Freshwater fishes	12	3
Saltwater fishes	61	3
Saltwater molluscs	9	158
Saltwater decapods	18	5

Tobacco in all its forms contains appreciable amounts of cadmium. Since the absorption of cadmium from the lung is substantially greater than that from the gastrointestinal tract, smoking contributes significantly to total body burdens. American cigarettes (Menden, et al. 1972) have been found to contain 1.5 to 2.0 μg per cigarette and about 70 percent of this passes into the smoke (Nandi, et al. 1969). All data agree that 0.1 to 0.2 μg cadmium are inhaled for each cigarette smoked. Thus, smoking 20 cigarettes per day will result in the inhalation of about 3 μg. It has been pointed out that workers handling cadmium compounds may contaminate their cigarette or pipe tobacco and further augment the high metal load contributed by smoking (Piscator, 1976).

Ambient air is not a significant source of cadmium exposure for the vast majority of the United States population. Data from the National Air Sampling Network have been summarized by Tabor and Warren (1958) and Schroeder (1970). Data collected in 1966 in 58 urban and 29 nonurban areas showed a range of concentrations of 2 - 370 and 0.4 - 26 ng per cubic meter, respectively. The data emphasize that nearly all airborne cadmium is due to man's activities. Highest concentrations are consistently found in industrialized cities and in the vicinity of smelting operations (Fleischer, 1974). In areas where there are no such sources of airborne cadmium pollution the levels observed have generally been around 0.001 $\mu g/m^3$, which leads to an average inhaled amount of approximately 0.02 - 0.03 µg per day for adults. In those cities with the highest levels of cadmium air pollution, i.e. up to approximately 400 ng/m^3, the maximum amount inhaled could rise on extreme occasion to 8.0 µg per day. As controls on emissions continue to tighten, intake via the respiratory route is expected to diminish.

Drinking water also contributes relatively little to the average daily intake. A survey of 969 U.S. community water supply systems, representing 5 percent of the national total, revealed an average cadmium concentration of 1.3 µg/l. Only three systems exceeded concentrations of 10 µg/l. Of 2,595 distribution samples taken during this same survey (McCabe, 1970) only four samples exceeded the 10 µg/l standard with the maximum sample having a concentration of 0.11 mg/l. Apparently an occasional water source is aggressive enough to cause some dissolution of metal from distribution piping, i.e. galvanized pipe. Most analyses of sea waters have reported average concentrations of 0.1 - 0.15 µg/l (Fleischer, 1974). Since this is less than fresh water sources entering the sea and far below the levels expected from solubility factors it has been suggested that cadmium is effectively removed by co-precipitation with or adsorption on clays, hydrous manganese oxide, or phosphorites (Posselt, 1971). Based on the above community water supply study and an average adult consumption rate of 2 liters/d, drinking water sources probably contribute not more than 3 - 4 µg/d to the total average cadmium intake.

Very little is known concerning the absorption of cadmium compounds through the skin and only the chloride salt has been studied (Skog and Wahlberg, 1964; Wahlberg, 1965). Maximum absorption of 1.8 percent over 5 hours was observed when a cadmium concentration of 26 gm/l was applied. At lower concentrations less than 1 percent absorption occurred. Since these levels are higher by a factor of approximately 20 million than household waters used for washing or bathing there seems to be virtually no risk of significant absorption through the skin. However, it should be pointed out that human studies have apparently not been done. Wastewater, indirectly, may play a considerably greater role since cadmium may enter the food chain from contaminated water used to irrigate fields producing crops for human consumption.

PHARMACOKINETICS

While ingestion constitutes the major part of human intake only a small propotion, i.e., approximately 5 percent, is absorbed, the rest passing directly into the feces. Gastrointestinal absorption is influenced by a number of dietary factors. Diets low in calcium lead to significantly higher levels of absorption and deposition of cadmium into intestinal mucosa, liver, and kidneys (Washko and Cousins, 1976) and corresponding decreases in fecal excretion. Cadmium increases the urinary excretion of calcium without affecting the excretion of phosphorus (Itokawa, et al. 1978). Cadmium inhibits the *in vitro* uptake of calcium from the rat duodendum, but calcium was not shown to have an inhibitory effect on the *in vitro* uptake of cadmium (Hamilton and Smith, 1978).

While confirming the *in vitro* inhibitory effect of cadmium on intestinal calcium absorption it has been recently demonstrated that the *in vivo* treatment of rats with cadmium, either acutely or chronically, does not decrease intestinal calcium absorption (Yuhas, et al. 1978). Diets deficient in vitamin D lead to increased cadmium absorption (Worker and Migicovsky, 1961). Low protein diets also lead to considerably higher levels of cadmium in various organs irrespective of the calcium content of the diet (Suzuki, et al. 1969). Similarly, deficiencies of zinc, iron, and copper have been shown to enhance cadmium uptake and subsequent adverse effects (Banis, et al. 1969; Bunn and Matrone, 1966; and Hill, et al. 1963). Ascorbic acid deficiency also promotes cadmium toxicity (Fox and Fry, 1970). The complex relationships between cadmium and various heavy metals and nutrients has been reviewed by Bremner (1974).

Human studies using ^{115m}Cd given orally have yielded absorption values of 6 percent (range 4.7 - 7.0 percent) and 4.6 (range 0.7 - 15.6 percent) (Rahola, et al. 1973; McLellan, et al. 1978). In the latter study, total body counting was used to determine cadmium absorption in 14 healthy subjects aged 21-61 years. A trivalent chromium ($CrCl_3$) marker, which is poorly absorbed from the gastrointestinal tract, was given along with ^{115m}Cd, assuming that unabsorbed cadmium would have the same transit time as chromium. The average body retention of radiocadmium determined between 7 and 14 days after the disappearance of the chromium marker from the body was 4.6 percent with a standard deviation of ± 4 percent. Various animal experiments have usually given lower oral absorption figures, i.e. approximately 2 percent, for ingested cadmium (Friberg, et al. 1974).

In contrast to ingestion, a relatively large proportion of respired cadmium is absorbed and inhalation represents a major mode of entry into the body for smokers and occupationally exposed persons. The fate of inhaled cadmium, in common with other respirable pollutants, depends upon particle size, solubility, and lung status. When a large proportion of particles are in the respirable range and the compound is relatively soluble, 25 percent of the inhaled amount may be absorbed. Cadmium fume may have an absorption of up to 50 percent and it is estimated that up to 50 percent of cadmium in cigarette smoke may be absorbed (WHO Task Group, 1977; Elinder, et al. 1976). Retrograde movement of particulate cadmium due to mucociliary transport may lead to eventual swallowing and gastrointestinal tract absorption.

Most studies on the transport and tissue distribution following absorption have been done in animals. Following intravenous or intraperitoneal administration most of the cadmium is initially found in the blood plasma. After 12-24 hours the plasma is cleared and most of the cadmium has entered erythrocytes which contain the metal-binding protein, metallothionein. With repeated administration the red cell content becomes many times greater than the plasma. Further distribution within the body is dependent on the elapsed time since absorption (U.S. EPA, 1975b).

Irrespective of the route of entry, cadmium is principally stored in the liver and kidneys with higher levels initially found in the liver. Following single exposures relocation occurs and liver concentrations eventually are exceeded by the renal cortex. Repeated exposures result in eventual high concentrations in both organs. Continued exposure eventually leads to a level of about 200-300 mg/kg wet weight in the renal cortex, after which pathologic changes occur which result in increased excretion of cadmium and protein in the urine, and no further accumulation occurs (WHO Task Group, 1977). The accumulation in the liver and kidneys seems to be mainly dependent on the storage of cadmium in association with the cadmium-binding protein, metallothionein (Chen, et al. 1975; Nordberg, et al. 1975).

Cadmium, unlike many trace metals, has no known function in normal metabolic processes. Recently there has been some speculation that cadmium may be an essential trace element. It has been reported that cadmium deficient animals respond with significant growth effects when cadmium salts are added to a basal diet. These effects are said to be dose dependent, consistent, and reproducible. In addition, glucose -6- phosphatase dehydrogenase may be activated by cadmium (Cadmium Research Digest, 1977). Confirmation of these findings, while of great scientific interest, would not lessen the need to control potential toxic exposures to the element. The factor which makes cadmium contamination of the environment a particularly serious hazard from the human health standpoint, is its pronounced tendency to bioaccumulate. Elinder and Kjellstrom (1977) have compared renal cadmium levels in specimens taken in recent autopsies (57 μg/gm dry weight) with specimens collected in the last century (15 μg/gm dry weight). These data indicate that cadmium body burdens are increasing, perhaps reflecting increased general environmental exposure to the element. A review of a great number of studies indicates that the total body burden of cadmium in humans increases with age, (Friberg, et al. 1974) from very minimal levels at birth ($<$ 1 ug), (Henke, et al. 1970) to an average of up to 30-40 mg by the age of 50 in non-occupationally exposed individuals (Friberg, et al. 1974). About 75 percent of this accumulation is found in the kidneys and liver, the kidneys containing approximately one-third of the average body burden with the highest levels localized in the renal cortex. In general, the liver continues to concentrate cadmium until the late decades of life while kidney concentrations increase to the fourth decade, peak, and steadily decline from the sixth decade (Gross, et al. 1976). The pancreas and salivary glands also contain considerable concentrations of cadmium while the brain and bone acquire only very small quantities (Nordberg, 1974). Age appears to have significant effects on how cadmium distributes after absorption. Using $^{115m}CdCl_2$ in rats, Kello and Kostial (1977) demonstrated that cadmium whole body retention declined with increasing age. Young animals had disproportionately more cadmium in their kidney and blood than older animals and correspondingly less accumulation in the liver. Smokers have an appreciably greater body burden of cadmium than non-smokers. The average concentration in the renal cortex is approximately doubled in smokers (Elinder, et al. 1976; Hammer, et al. 1973). It is of interest that in Japan where the average diet contains appreciably more cadmium than in Western countries, the metal could be detected in 57 percent of human embryos of 31 to 35 days gestation and this figure increased to 80 percent during the second trimester (Chaube, et al. 1973). Blood levels in newborn babies are correlated with maternal blood levels, but average only 50 percent of the maternal levels (Lauwerys, 1978). In environmentally exposed children, urinary cadmium levels were a more sensitive indicator of exposure than blood cadmium (Roels, et al. 1978).

In non-occupationally exposed persons the mean level of cadmium in the blood is usually less than 1 μg/100 ml. Children without known exposure, aged 2 months to 13 years (average 4.9 years), are reported as having slightly lower levels, i.e. 0.66 μg/100 ml (Smith, et al. 1976). Smokers are reported as having blood cadmium levels 50 percent greater than non-smokers (Einbrodt, et al. 1976).

Several reports indicate that urinary excretion of cadmium is approximately 1-2 μg/day in the general population (Imbus, et al. 1963; Szadkowski, et al. 1969). There is a modest increment in urinary levels with age (Katagiri, et al. 1971). Urinary excretion may be markedly elevated in exposed workers including those without renal damage (Friberg, et al. 1974). If renal tubular dysfunction should occur due to cadmium accumulation, the rate of urinary cadmium excretion will further increase, which in turn results in a considerable decrease in renal cadmium levels, even though irreversible tubular damage has already occurred (Kjellstrom, 1976). It should be mentioned that renal levels fall after age 50 even in "normal" persons and decreased renal levels are not necessarily due to cadmium-induced renal disease.

Fecal excretion appears to closely reflect the dietary intake (Tipton and Stewart, 1970; Kojima, et al. 1977) as might be anticipated from the previously discussed absorption data. Smokers have a slightly increased fecal excretion rate averaging 3.2 µg/d (Kjellstrom, et al. 1978a). It is unknown as to how much fecal cadmium may be derived from intestinal epithelium or biliary excretion. Saliva contains up to 0.1 µg/g cadmium (Driezen, et al. 1970) and may contribute significantly to fecal excretion since a normal adult will secrete 1,000-1,500 ml/d. The amount of gastrointestinal reabsorption is unknown. Biliary excretion has been studied by Stowe (1976) who observed normal rat bile to contain 22 ± 3 ppb cadmium. Rats fed 100 ppm cadmium excreted bile containing 58 ± 6 ppb. Less than 0.1 percent of subcutaneously-injected cadmium was excreted in the bile within the first 5 hours following administration.

Hair is a minor excretory pathway and may contain from 0.5 to 3.5 µg/g (Friberg, 1974). In rats, continued exposure to cadmium in drinking water leads to initially high hair levels, which decline dramatically with continued administration; and it has been concluded that hair cadmium would not be useful in estimating either concentrations in vital organs or degree of organ damage (Brancato, et al. 1976). In infancy human hair has been shown to have relatively high levels of cadmium which thereafter decline throughout life (Gross, et al. 1976). While positive correlations have been reported between environmental levels (Hammer, et al. 1971) and occupational exposure and visceral organ levels (Oleru, 1975) these associations are generally too weak to permit accurate quantitative assessments of human exposure to cadmium.

Estimates of the biologic half-time of absorbed cadmium have been derived in a number of ways, i.e., by theoretical metabolic balance studies, determining the half-time in blood or urine, and by measuring the decrease in whole-body retention of isotopic cadmium.

Studies on the half-time in urine (Sudo and Nomiyama, 1972) or blood (Tsuchiya, 1970) have given values of 200 days and 1 year, respectively, for former occupationally-exposed workers. The number of workers studied was very small. Obviously, this approach may not reflect the total body burden of cadmium, some of which may be very tightly bound in various tissues. Also, these subjects are not representative of normal environmental exposure in which urine may reflect the total body burden (Tsuchiya, et al. 1976), but of current exposure when such exposure has been or is high (Lauwerys, et al. 1976). Blood also is thought to best represent current exposure (Lauwerys, et al. 1976). Direct comparison of urinary excretion levels and estimated body burden have also been performed using

Japanese, American and German data. These data suggest a half-time of 13 - 47 years. Similar time frames have been found using more complex metabolic models and Friberg (Friberg, et al. 1974) has concluded that the biologic half-time is probably 10 - 30 years. These methods suffer the disadvantage that actual body burdens cannot be ascertained for the living subject and are assumed to be the same as averages derived from autopsy studies.

Only two human studies using radioisotopes are available. Rahola (Rahola, et al. 1973) stated it was not possible to accurately determine a biologic half-time, but provided a shortest estimate of 130 d and a longest of infinity. In a single human subject for whom the figure could be calculated the biologic half-time was 100 d (McLellan, et al. 1978).

From the foregoing, it is obvious that the data are not in good agreement regarding cadmium half-time with estimates varying at least 100-fold (months vs. decades). Since this is a critical issue in terms of maximum daily limits for standard-setting purposes, it is essential that more new data be generated to resolve this facet of cadmium metabolism. Nomiyama, et al. (1978) has demonstrated in Rhesus monkeys that cadmium half-time is inversely related to the oral intake of the element. This may explain some of the wide variation seen in human studies.

In summary, from the exposure, intake, absorption, and excretion data it appears that most persons exposed to cadmium in the general environment are in an approximate cadmium balance. Autopsy data suggest a slight positive balance until approximately age 50 after which a negative balance ensues. The reasons for this decline are unknown. It is unrelated to the presence or absence of renal disease, but may be due to the lessened intake of food as caloric needs also decline in later life. It has also been suggested that the observed decrease may be an artifact related to the possibility that older persons may have been exposed to far lower cadmium levels during their youth (Hammer, et al. 1973).

EFFECTS

Acute Effects

When adminstered orally cadmium acts as an emetic in both man and subhuman species. Cadmium metal is quite soluble in weak acids such as those commonly found in many foods and beverages. Organic cadmium salts may be transformed upon contact with gastric hydrochloric acid into cadmium chloride which has an inflammatory action on the mucus membranes of the stomach and intestine (Browning, 1969). Oral administration of cadmium produces emesis at a concentration of about 400 ppm (23 mg/Kg) in food (Schwarze and Alsberg, 1923). These authors cite the case of Burdach who induced vomiting with one-half grain of cadmium sulfate, which contains about 15 mg of cadmium.

The oral LD_{50} in rats varies only slightly with the cadmium compound employed, i.e. oxide, 72 mg/Kg; chloride, 88 mg/Kg; and fluorosilicate, 100 mg/Kg. 250 mg/Kg has been given as the lowest oral dose producing death in rats using cadmium fluroborate. The LD_{50} for guinea pigs given cadmium fluoride is reported to be 150 mg/Kg (Toxic Substances List, 1974). More complete acute toxicity data is given in EPA-560/3-75-005 (U.S. EPA, 1975a). The lethal oral dose of cadmium for man is not known (Thienes and Haley, 1972).

Because of its acid solubility and formerly widespread usage in plating metal utensils and containers cadmium has been responsible for numerous outbreaks of acute poisoning in the past. Some 689 cases of cadmium poisoning were reported within the 5-year period 1941-1946 (Fairhall, 1957) and doubtless numerous other undiagnosed and unreported cases also occurred. Largely as a result of these outbreaks various sanitary codes and national standards have been amended to prohibit the use of cadmium in any article used for food or drink preparation or storage. The most significant clinical feature of acute cadmium poisoning is the rapidity with which symptoms become apparent following ingestion. Most persons become symptomatic within 15 to 30 minutes after ingesting either food or drink containing toxic amounts of the metal. The symptoms typically include persistent vomiting, increased salivation, choking sensations, abdominal pain, tenesmus, and diarrhea (Browning, 1969; Frant and Kleeman, 1941). The dose causing such symptoms has been estimated to be within the range of 15-30 mg (Gleason, et al. 1969; Nordberg, et al. 1974).

Because numerous cases of acute industrial poisoning from cadmium have occurred from dust or fume generated by the burning, heating, welding, melting, or pouring of cadmium metal, cadmium alloys, or cadmium plate the respiratory tract effects have been well documented (Kazantzis, 1963a).

Symptoms from acute poisoning by cadmium oxide fumes appear 4-6 hours after exposure and include cough, shortness of breath and tightness of the chest. Pulmonary edema may ensue within 24 hours, often to be followed by bronchopneumonia. Most cases are resolved within a week. The fatality rate ranges between 15 and 20 percent (Bonnell, 1965). Later effects from acute overexposure include pulmonary fibrosis

(Health, et al. 1968), permanently impaired lung function (Townshend, 1968) and disturbed liver function (Blejer, et al. 1971). Barrett and Card (1947) estimated that the lethal dose for a man doing light work would not exceed 2,900 min. mg/m^3. From these figures it may be estimated that a lethal exposure to cadmium fume may result from breathing a concentration of approximately 5 mg/m^3 over an 8-hour period. In Blejer's fatal case it was thought that the atmospheric concentration exceeded 1 mg/m^3.

Ansomia is a well described defect in those employed in the cadmium industry and correlates with the appearance of proteinuria, i.e. both depend upon length of service (Potts, 1965; Friberg, 1950; Adams and Crabtree, 1961; Tsuji, et al. 1972). Phil and Parkes (1977) noted elevated cadmium and lead levels in the hair of children with learning disability.

Chronic Effects

A host of chronic effects attributed to cadmium exposure have been reported by numerous investigators over the past three decades. Without doubt, at least in terms of human effects, the two cardinal pathologic lesions associated with cadmium are pulmonary emphysema and renal tubular damage.

Friberg (1948, 1950) was the first to note emphysema in his now classic studies of workmen exposed to cadmium iron oxide dust in a Swedish alkaline battery factory. Since then numerous investigators have confirmed and expanded upon these initial findings (Paterson, 1947; Baader, 1952; Lane and Campbell, 1954; Buxton, 1956; Smith, et al. 1960;

Kazantzis, et al. 1963a; Potts, 1965; Holden, 1965; Lewis, et al. 1969; Snider, et al. 1973; Lauwerys, et al. 1974; and Smith, et al. 1976).

A possible mechanism for cadmium emphysema has been suggested by Chowdhury and Lauria (1976) who noted that the addition of cadmium to human plasma caused an inhibition of alpha-1-antitrypsin with a decrease in trypsin inhibitory capacity. Other metals had little or no effect at equimolar concentrations. Persons with congenital alpha-1-antitrypsin deficiency have a marked increased risk of emphysema and cadmium may stimulate or augment this defect.

Based on data from studies of the acute pulmonary effects, the studies of long-term industrial exposure, and the absence of contradicting animal data it seems apparent that cadmium induced emphysema is related only to the inhalation route of exposure. Apparently no studies have been done relating the incidence of emphysema in the general population to varying ambient levels of airborne cadmium.

There is general agreement that renal tubular damage is the most important chronic effect of cadmium exposure irrespective of route. The hallmark of this injury is the appearance of a low molecular weight (20,000-25,000) protein in the urine (B_2-microglobulin). Industrial studies have shown that proteinuria is not only much more common than emphysema, but also that it appears after shorter periods of exposure. This protein is not the same as that excreted after conventional kidney damage and doesn't react in the usual laboratory tests designed to detect urinary protein

(Browning, 1969). First reported in 1948 by Friberg in workers exposed to cadmium oxide dust, B_2-microglobulin has subsequently been reported in the urine of workers exposed to other forms of cadmium and in the urine of animals experimentally exposed. As cadmium accumulates in the kidney it inhibits tubular reabsorption resulting in proteinuria (Berggard and Bearn, 1968). Other signs of renal tubular dysfunction resulting from cadmium exposure are glycosuria, aminoaciduria, and changes in the metabolism of calcium and phosphorus (Kazantzis, 1963a). The dysfunction rarely progresses to renal failure, but hypercalcinuria may occasionally lead to a negative calcium balance and to osteomalacia (Nicaud et al. 1942; Adams, et al. 1969).

High levels of proteinuria have been found in Itai-itai disease patients where increased excretion is strongly correlated to residence time in exposed areas and the use of cadmium contaminated river water (Kjellstrom, et al. 1977a). Tsuchiya, et al. (1978) has found that B_2-microglobulin excretion is highly correlated with aging in both high and low cadmium exposure population groups. Kjellstrom, et al. (1977a,b,c) has attempted to determine a dose response between B_2-microglobulin excretion and cadmium in air (estimated concentration 50 $\mu g/m^3$). He determined the geometric average B_2-microglobulin concentration to be 84 $\mu g/l$ in normal unexposed persons with 95 percent confidence limits of 24-290 $\mu g/l$. Using the upper 95 percent limit he found an elevated excretion prevalence of 19 percent for workers with 6-12 years exposure.

Smokers were also noted to have about 2 to 3 times the prevalence of elevated excretion found for non-smokers. This applies to both the industrially-exposed smokers as well as non-exposed workers. Women are noted to have a lower prevalence than men and this is attributed to sex differences in smoking habits.

Kjellstrom (1977a) is careful to point out that elevated chronic excretion of B_2-microglobulin does not equate with clinically significant proteinuria and that its definition was designed for comparative epidemiological purposes. While pointing out that the relationship of cadmium proteinuria to life expectancy is unknown Kazantzis (1977) believes it is evidence of a critical effect. Adams, et al. (1969) long-term observations indicate that some men have had proteinuria for many years without serious impairment of glomerular filtration. He notes that retired men do not seem to have more serious renal disease than those still at work and that there is no good evidence of progression to terminal renal failure. It would seem reasonable to conclude that in the vast majority of cases mild or moderate excretion of B_2-microglobulin is a relatively benign condition. On occasion the renal lesion may be severe enough to produce osteomalacia and multiple fractures as in Itai-itai disease. However, in all such cases (Friberg, 1974; Nicaud, et al. 1942; Adams, et al. 1969) there appear to have been multiple dietary deficiencies (calcium, protein, Vitamin C, Vitamin D) in addition to an excessive cadmium exposure. For example, Itai-itai disease occurs almost exclusively in grand multiparous women over the age of 50 who live predominantly on a rice diet with a high (600 μg/d) cadmium content. The Japanese government has monitored for new cases of Itai-itai disease since 1969. Since then no new patients with the disease have been found, although the frequency of tubular dysfunction and urinary cadmium are higher in polluted than in control areas (Shigematsu and Yoshida, 1978). Nicaud's cases occurred under wartime factory conditions in France. It seems apparent that multiple nutritional deficiencies may be more important than cadmium in producing this complex disorder. While the bone changes (osteomalacia) have been assumed to be secondary to the renal defect it has been shown in animals that cadmium may directly cause osteoporotic bone changes (Yoshiki, et al. 1975). Such evidence implies that certain segments of the population living on subsistence diets may well be at increased risk from cadmium.

Based on animal and limited human data, the critical cadmium concentration in the renal cortex has been estimated to be about 200 mg/Kg wet weight (WHO, 1977; Friberg, et al. 1974; Nordberg, 1976). The 28 human cases used to support this figure show an extremely large variation in concentration. Nomiyama (1977a) points out that this figure should be determined from data in cases where proteinuria was the only finding, i.e. exclude those cases with obvious pathologic changes since in long standing severe disease the net amount of cadmium may be decreased from that at disease inception. In the eight cases with proteinuria only, the concentration varied from 150 to 395 mg/Kg wet weight with the exception of a single specimen with a level of 21 mg/Kg wet weight. Four had levels in excess of 300. He suggests that 300 mg/Kg wet weight is a more appropriate critical level. This is supported by his findings on monkeys (Nomiyama, et al. 1977b).

Kjellstrom (1977b,c) has used the figure of 200 mg/Kg wet weight of cadmium in the renal cortex as an estimate of the level where tubular damage occurs in constructing a metabolic model from which to calculate a dose-response corresponding to daily intake. His model gives lower values for Japanese than Europeans because of the former's smaller average body and kidney weight. For Europeans the expected response rate, i.e. the proportion of the population with evidence of renal tubular damage, as manifested by excessive B_2-microglobulin excretion for a given daily cadmium intake, is expected to approximate the following sequence: 0.1 percent-32 µg Cd/d; 1.0 percent-60 µg Cd/d; 2.5 percent-80 µg Cd/d; 5.0 percent-100 µg Cd/d; 10 percent-148 µg Cd/d; and 50 percent-440 µg Cd/d. These estimates are for non-smokers. Smoking will reduce the above allowable intake from food by approximately 25 µg/d for each package of cigarettes smoked. Water consumption will reduce the allowance for food on a ug for ug basis assuming equilivent gastrointestinal absorption for food and water. Other sources of cadmium would normally have only very minor effects. If the value for renal damage averages closer to 300 mg cadmium/Kg wet weight of cortex instead of 200 this would result in a proportional increase in allowable daily intake.

In addition to the generally conceded major toxic effects of cadmium in man it has been hypothesized that exposure to ambient cadmium levels may be an important factor in the etiology of essential hypertension. Three major lines of evidence have been set forth to support this thesis: (1) in some animal experiments cadmium has induced hypertension; (2) hypertension is positively correlated with the ingestion of soft drinking waters, which often contain higher concentrations of heavy metals than hard waters; and (3) that hypertension patients have higher renal, bone, and body fluid cadmium levels (Schroeder and Vinton, 1962; Schroeder, 1964a,b,1965,1966; Schroeder and Balassa, 1961; Crawford, et al. 1968; Lener and Bibr, 1971; Thind and Fischer, 1976; Crawford, 1973; Perry, 1972). Hypertension is not always found in animals exposed to cadmium (Lener and Bibr, 1971) and this effect shows variability among strains and is related to the amount of sodium chloride in the diet (Nordberg, 1974). In rats, genetic composition is a critical determinant for the induction of hypertension by cadmium. Selective inbreeding has led to animals which are completely resistant to this effect (Ohanian and Iwai, 1978). Most of the studies relating elevated tissue levels of cadmium to hypertension (Schroeder, 1965; Perry and Schroeder, 1955; Thind and Fischer, 1976; Lener and Bibr, 1971; Glauser, et al. 1976) were carried out before the impact of smoking on cadmium accumulation was appreciated, or have tended to ignore this factor. Much careful work now tends to indicate that the association between hypertension and cadmium may be a spurious one. Morgan (1972) in a large autopsy series was unable to correlate hypertension and mean renal cadmium. Similarly, Lewis, et al. (1972) failed to find a relationship between renal levels of cadmium and hypertension. Beevers, et al. (1976) were unable to find any significant differences in blood cadmium between 70 hypertensive patients and 70 controls who were matched for age and sex. Østergaard (1977) compared renal cadmium tissue levels in 39 hypertensive and 43 normotensive subjects. In this series only subjects 45-65 years of age were studied to minimize the effects of age on cadmium accumulation. The data suggest that hypertensive renal disease may enhance cadmium excretion. Szadkowski's (1969) study measured the urinary excretion of cadmium in a large series of persons and could find no relationship between cadmium excretion and hypertension. Very significantly, epidemiologic studies of industrially exposed persons have failed to support the concept that cadmium is a significant factor in human hypertension (Friberg, et al. 1974; Holden, 1969). In addition, Japanese patients with Itai-itai disease do not have hypertension (Perry, 1972; Nogawa and Kawana, 1969).

Besides the effects previously discussed, chronic exposure to cadmium has been suggested to play a causative role in a number of other pathologic changes in man. These studies are usually in the form of case reports and often have been reported by only a single author or group. In general, these effects when considered individually are of lesser importance to human health, but collectively represent possibly an important gap in the knowledge of concerning cadmium toxicity. A brief discussion of several of the more significant of these adverse effects follows.

Friberg (1950) noted abnormal liver function tests in his classic study first documenting emphysema and kidney damage. Blejer (1971) also found such changes in cases of acute overwhelming exposure. Other authors have commented upon the rarity of such findings (Bonnell, 1965; Kazantzis, et al. 1963a).

Renal stones have been reported for both Swedish and British workers (Ahlmark, et al. 1961; Adams, et al. 1969). These have occurred in both proteinuric and non-proteinuric workmen. Since renal stones are a common problem more definitive industry wide studies are needed to determine the true prevalence of this problem.

Moderate anemia has been described in a number of studies (Friberg, 1950; Hardy and Skinner, 1947). This effect is also seen in animals with experimental cadmium poisoning (Prodan, 1932).

Other reported effects include changes in lipids (Schroeder and Balassa, 1965), rhinorrhea (Baader, 1952), bone marrow changes (Cotter and Cotter, 1951), dental caries (Hardy and Skinner, 1947), and non-specific nervous system signs and symptoms (Vorobjeva, 1957).

Koller has published a series of papers describing various forms of immunosuppression in experimental animals treated with cadmium, i.e., lower neutralizing titers against pseudorabies virus, decreased antibody synthesis, decreased levels of IgG, etc. (Koller, 1973; Koller, et al. 1975, 1976). In animals, cadmium has been shown to affect various enzymes which control blood glucose levels. The significance of these findings in terms of human health is conjectural.

Compounds Antagonistic to Cadmium

A wide range of chemical and natural substances have been shown to modify the toxicologic properties of cadmium. This effect has been seen in highly varying biologic systems and appears to be in many instances due to competition with other metallic elements for protein-binding sites.

Cadmium toxicity is decreased by other metal ions. In animals zinc has been shown to prevent cadmium-induced testicular damage and teratogenic effects (Parizek, 1957; Parizek, et al. 1969a; and Ferm and Carpenter, 1967). It reportedly reduces cadmium's ability to induce tumors (Gunn, et al. 1963, 1964) and it reduces cadmium-induced growth inhibition. Copper has also been shown to reduce mortality and anemia induced by cadmium in various species and to prevent the degenerative effects of cadmium on aortic elastin (Hill, et al. 1963; Bunn and Matrone, 1966). Starcher (1969) has shown that cadmium decreases intestinal copper uptake, probably through competition for binding sites.

The anemia produced experimentally in fowl fed high cadmium diets is remedied by increases in iron or ascorbic acid intake (Hill, et al. 1963; Fox and Fry, 1970; Fox, 1975). The protective effect of these agents may be mediated by increased iron absorption in the intestine (Freeland and Cousins, 1973). The situation seems analogous to copper.

There is mounting evidence that elevated cadmium intake can adversely affect calcium metabolism (Bremner, 1974). Bone disease was first recognized as a toxic manifestion of cadmium during World War II (Nicaud, et al. 1942) and osteomalcia is an important component of Itai-itai disease. Two explanations are attractive: (1) that the bone disease is secondary to cadmium induced renal tubular dysfunction or (2) that cadmium accumulation is in part a consequence of diets deficient in calcium and Vitamin D. The latter explanation seems the most appropriate (Larsson and Piscator, 1971). The osteoporotic changes may arise from an inhibitory effect of cadmium on the renal synthesis of 1,25-dihydroxy cholecalciferol, which is the active form of Vitamin D_3. This inhibition has been demonstrated *in vitro* (Feldman and Cousins, 1973).

Rats which have been pre-treated with cadmium show decreased intestinal absorption of calcium and markedly increased fecal calcium excretion. These animals also demonstrate a 30 percent decrease in calcium incorporation in bone and the investigators suggest these effects are important in the etiology of Itai-itai disease (Ando, et al. 1977; Kobayashi, 1970).

The effects of protein in reducing cadmium toxicity have previously been mentioned. It has been suggested that the protective effects are actually due to increased availability of zinc and/or iron (Fox, et al. 1973).

Cadmium itself will induce tolerance if given by small repetitive injections (Nordberg, 1971). This effect is postulated to be due to the stimulation or induction of a protective protein, metallothionein. Probst, et al. (1977) have demonstrated that hepatic metallothionein concentrations increase in proportion to the cadmium pretreatment dose and found a positive correlation between dose related increases in hepatic metallothionein and cadmium LD_{50} values. This cadmium binding protein apparently plays a key role in cadmium detoxication. It contains a high (30) percentage of cysteinyl residues and hence has an extreme affinity for metal binding. About one metal ion is bound per three - SH groups and it may contain up to 9 percent metal. Zinc usually occupies the vast majority of binding sites, but may be replaced by various other cations, i.e., cadmium, cobalt, mercury, copper, etc. The protective effect of prior administration of zinc against cadmium has been attributed to the increased accumulation of hepatic and renal cadmium as metallothionein. The inactivity of cadmium-metallothionein complexes in reducing SH enzyme activity and 1,25-dihydroxycholecalciferol synthesis suggests that the bound form is inactive (Webb, 1975; Feldman and Cousins, 1973). As might be anticipated cysteine similarly protects against cadmium induced testicular necrosis (Gunn, et al. 1968). The synthesis of metallothionein-like proteins can be induced by at least two essential elements, i.e. zinc and copper, and the protein may have a fundamental role in the metabolism of these elements. The induction by cadmium and mercury may therefore simply be a fortunate circumstance occasioned by chemical similarities (Webb, 1972a). Beryllium, manganese, barium, strontium, tin, arsenic, selenium, chromium, and nickel administration have been shown not to influence liver or kidney levels of metallothionein-like protein whereas cobalt and iron increase liver levels and bismuth increases renal tissue concentrations (Pitrowski, 1976).

Selenium is yet another protective element which is able to prevent lethal cadmium effects or the induction of testicular damage in rodents (Gunn, et al. 1968b; Parizek, et al. 1969a). Conversely, cadmium is able to reverse both the lethal and the growth retardation induced by toxic quantities of selenium (Hill, 1974).

Cadmium administration also causes the elevation of a number of enzymes (hepatic pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose 1,6-disphosphatase and glucose 6-phosphatase), increases the concentrations of hepatic cyclic adenosine monophosphate and blood glucose while simultaneously reducing serum insulin. The administration of selenium prevents the elevation of the cadmium hepatic gluconeogenic enzymes and ameliorates the hyperglycemia, hypoinsulinemia, and glucose intolerance. Selenium does not, however, alter the cadmium induced elevation of hepatic cyclic AMP levels. (Merali and Singhal, 1975). Selenium causes an increase in the biliary excretion of cadmium (Stowe, 1976). This contrasts with zinc which causes a significant reduction of biliary cadmium excretion. The mechanisms involved in the protection by selenium against cadmium toxicity have been investigated by Chen, et al. (1975) and appear to be the result of cadmium diversion by selenium from low-molecular weight proteins to less critical higher molecular weight moieties. Both selenium and cadmium are equally bound in a 1:1 ratio in plasma protein fractions ranging in size from 130,000 to 420,000 daltons (Gasiewicz and Smith, 1976).

The number of complex interactions with various metals and nutrients suggests strongly that certain sectors of the public will in all likelihood be at greater risk from cadmium than the community as a whole. For example, cadmium may pose an increased hazard to those with anemia or for those in need of additional calcium, such as pregnant women or growing children. Cadmium may be more toxic for those living in areas where zinc deficiency is common, i.e. Egypt, Iran, etc. and where protein deficiency states such as Kwashiorkor are common, i.e. many "third-world" countries. Studies of these and other sensitive groups is only now beginning.

Reproductive Effects and Teratogenicity

Relatively low doses of parenterally administered cadmium have been shown to have profound effects upon the reproductive abilities of various species of experimental rodents.

Parizek and Zahor (1956) first noted in rats that a single small dose of cadmium chloride (2 mg/Kg) given subcutaneously results in testicular hemorrhage and complete testicular necrosis. Subsequently, a similar effect was noted in rabbits, hamsters, guinea pigs and mice. (Parizek, 1957; Meek, 1959). This effect is mediated by selective damage to the internal spermatic artery and pampiniform venous plexus rather than by a direct effect on testicular tissue (Gunn, et al. 1963b). This renders the animal permanently sterile (Parizek, 1960). Following necrosis the majority of the seminiferous tubules remain atrophic and only a few contain germinal epithelium. The Leydig cell component of the testis regenerates sporadically throughout the tissue resulting in both hyperplastic nodules and Leydig cell tumors of variable histologic appearance. These tumors exhibit a moderate degree of pleomorphism and occasional mitotic figures (Roe, et al. 1964). There is no difference in testicle size between cadmium treated mice and controls, but the seminal vesicles and other accessory sex organs decrease in size implying a decreased secretory capacity of testosterone from the damaged Leydig cells (Nordberg, 1975b). This effect is prevented by the simultaneous administration of zinc with cadmium (Gunn, et al. 1963). It should be pointed out that this effect is not seen in certain inbred strains of mice (Gunn, et al. 1965; Lucis and Lucis, 1969) and apparently identical Leydig cell tumors (interstitial cell tumors) are caused in rodents by a variety of other agents besides cadmium, i.e., estrogenic substances (Andarvont, et al. 1957), implanted testicular fragments (Biskind and Biskind, 1945), minor testicular trauma (Malcolm, 1972), and ligation of the internal spermatic artery and vas deferens (Fels and Bur, 1958). Testicular necrosis and subsequent interstitial cell tumor formation due to cadmium apparently have not been observed in man. Necropsy and subsequent histologic examination of the testis in fatal cases of cadmium poisoning have revealed no abnormalities despite the passage of some days or years following exposure and death (Beton, et al. 1966; Blejer, 1971; Smith, et al. 1960).

Somewhat analogous effects have been observed in female rodents. Cadmium damages the ovaries of non-ovulating rats in persistent estrus and in prepubertal females (Parizek, et al. 1968b; Kar, et al. 1959). The lactating mammary gland is also affected by cadmium and important changes occur in the form of acinar necrosis, intralobular hyperemia, and interestitial edema. The effects on both ovary and mammary gland are prevented by the simultaneous administration of selenium (Parizek, 1968; Parizek, et al. 1968). Rats in late pregnancy are apparently more sensitive to cadmium than non-gravid animals or those immediately post-partum. A single dose of 2-3 mg/Kg of body weight given during the last 4 days of pregnancy results in a high mortality (76 percent) within 1 to 4 days of injection. On autopsy generalized visceral congestion, pleural effusion, enlarged kidneys, adrenal hemorrhage, and pulmonary thrombosis are prominent findings. No similar changes were seen in non-pregnant or immediately post-partum animals (Parizek, 1965).

In the pregnant rat cadmium results in a complete destruction of the fetal portions of the placenta and death of the fetuses (Parizek, 1964). In mice, of differing strains, embryos and fetuses show a wide range of sensitivity to cadmium induced embryotoxicity and death. Crosses between resistant and sensitive strains indicate an inherited pattern of sensitivity, with cadmium crossing the placenta in both strains, but less well in the more resistant animals (Wolkowski, 1976). Rodents have a hemochorial placenta and it is unknown whether higher species would be affected in a similar manner.

Schroeder and Mitchener (1971) have carried out three generation rodent studies with a number of trace elements. Cadmium in drinking water (10 ppm) resulted in "loss of the strain." In the F_1 generation 39 young deaths occurred and 25 runts were noted compared with none in the controls. In the F_2 there were two dead litters, 48 young deaths, three failures to breed and nine runts. Again, both runting and young deaths were statistically significantly increased. A congenital abnormality, sharp angulation of the distal third of the tail was seen in 16.1 percent of live offspring. Because of breeding failures the experiment was terminated after the F_2 generation. In contrast, Suter (1975) found no detectable fertility effects, except superovulation and larger than normal litters, in inbred mouse strains injected with 1 or 2 mg/Kg of cadmium chloride. Doses of 3 and 4 mg/Kg resulted in a very high immediate mortality rate. Dixon, et al. (1976) found no reproductive effects in rats supplied with drinking water containing 0.1 mg/l for 90 days.

While cadmium crosses the placental barrier quite poorly some passage definitely occurs. In rats this has been shown to be dose dependent and to increase with gestational age (Sonawane, et al. 1975). In the hamster, significant amounts of cadmium cross the placenta and enter the embryo by the 8th day of gestation, the time frame corresponding to the teratogenic effects seen in the species. Zinc can prevent these effects, but does not prevent the placental transfer of radioactive cadmium (Ferm, et al. 1969).

When cadmium is administered to pregnant hamsters on days 12-14 marked effects have been noted in the facial development of the offspring. Effects include unilateral and bilateral clefts of the palate, midline clefts through the nose, thyroglossal clefts, and anophthalmia (Ferm and Carpenter, 1967; Ferm, 1967). Mulvihill, et al. (1970) have suggested that this failure of fusion is due to a mesodermal deficiency rather than to delays in shelf transportation. Selenium has been shown to have a markedly protective effect against cadmium teratogensis in the hamster (Holnberg and Ferm, 1969). Similarly, cadmium administered to rats on gestation days 13-16 produced a dose related increase in anomalies, including micrognathia, cleft palate, clubfoot, and small lungs (Chernoff, 1973). In addition, the lung/body weight ratio was reduced indicating a specific retardation and not merely a reflection of differential organ growth rates and overall growth retardation. A single intravenous dose of 1.25 mg cadmium/Kg body weight given between the 8th and 15th days of gestation produces more than 90 percent fetal deformities in rats (Samarawickrama and Webb, 1978). The commonest anomaly was hydrocephalus with an incidence of 80 percent when the cadmium was given on day 10 of gestation. The mechanism of action of cadmium in producing teratologic effects, i.e. directly upon differentiating embryonic tissue or indirectly via effects on maternal tissues, remains unknown. However, it has been shown that low levels of cadmium which do not affect cellular growth can alter RNA metabolism in Chinese hamster ovary cells to a significant extent and

TABLE 2

Experiments in Tissue Culture Systems Using Cadmium

Authors	Cell Culture	Observations
Zasukhina, et al. (1975)	Rat embryo	+ Chromosomal aberrations
Rohr and Bauchinger (1976)	Chinese hamster fibroblasts	+ Chromatid aberrations
Casto, et al. (1976)	Hamster embryo	+ Persistent morphologic alternations; enhanced transformation by simian adenovirus 7; 8-azag-uanine resistance - unscheduled DNA synthesis
Shiraishi, et al. (1972)	Human leukocytes	+ Chromatid breaks, dicentric chromosomes
Paton and Allison (1972)	Human leukocytes and fibroblasts	-

it has been postulated that this may modify normal cell development and serve as a possible basis for teratogenic effects (Enger, 1976). The possibility of human teratogenicity has not been systematically examined and only one report (Tsvetkova, 1970) suggests such an effect. In this brief report children of women occupationally exposed to cadmium were found to have lower birth weights than 20 control infants. In view of the many factors which may contribute to lowered birth weight, i.e. parity, maternal weight, chronic maternal illness, socioeconomic conditions, maternal smoking, prenatal nutrition, etc., little credence can be placed on this report.

Mutagenicity

In the past decade cadmium has been studied in a variety of *in vitro* and *in vivo* test systems with somewhat conflicting results. Sunderman (1978) has recently reviewed *in vitro* experiments that may be relevant to metal carcinogenesis. The Environmental Protection Agency's Carcinogen Assessment Group has performed a similar review of these tests (U.S. EPA, 1977).

Cadmium has been reported to cause chromosomal or mitotic aberrations in mammalian tissue culture cell lines. These are summarized in Table 2. The majority of these studies suggest a cadmium effect. In addition, several *in vitro* studies in biochemical systems have now been reported.

Sirover and Loeb (1976) have studied 31 metal compounds *in vitro* using a system designed to detect infidelity of DNA synthesis. Both cadmium acetate and cadmium chloride demonstrated decreased fidelity, i.e. increased error frequency. Decreased fidelity of DNA synthesis *in vitro* has also been reported by Hoffman and Niyogi (1977) for cadmium, lead, cobalt, copper, and manganese. These investigators also found that these metals stimulated chain initiation of RNA synthesis at concentrations that inhibited overall RNA synthesis. Murray and Flessel (1976) have reported that *in vitro* addition of cadmium and manganese ions to solutions of synthetic polynucleotides caused pairing of noncomplementary nucleotides and have emphasized that direct metal-nucleic acid interactions may be responsible for neoplastic transformation by metals. Zinc and magnesium did not show this effect.

Friedman and Staub (1976) have studied cadmium and numerous other compounds to determine if mutagenic substances modify DNA replicative activity. In their assay the uptake into mouse testicular DNA of (^{3}H) thymidine is measured 3.5 hours after injection of the test compound. Cadmium treated (10 mg/Kg) mice showed a significant decrease (p .05) in (^{3}H) thymidine uptake in comparison to control animals. The effect was, however, much less than the inhibition caused by 3-methylcholanthrene and diethylnitrosamine. This inhibitory effect may be due to cadmium's ability to impair testicular blood supply and cause complete necrosis of the testis. The dose given was at least three-fold that required to induce this acute effect.

The results with cadmium in various microbial systems designed to detect mutations have shown quite mixed results (Table 3). McCann, et al. (1975) have reported that three of four metal carcinogens tested in the standard Ames test

TABLE 3

Mutagenesis Studies of Microbial Systems Using Cadmium

Author	Organism		Result
Nishioka (1975)	B. subtilis	+ -	Weak response ($CdCl_2$) $Cd(NO_3)_2$
Takahoshi (1972)	S. cerevisiae	+	Reported in CAG Assessment
Sunderman (1978)	S. typhimurium	-	Two independent investigators reported to Sunderman

have been negative. They do not name these metals, but suggest that the system is not favorable for bacterial absorption of metals because of the large amount of Mg salts, citrate, and phosphate in the minimal medium.

A fairly large number of studies now exist which have examined a variety of mammalian cells for cytogenetic abnormalities following exposure of the intact animal or man to cadmium (Table 4). Again mixed results have been obtained. It should not be forgotten that most of the studies on workers reflect a mixed exposure to zinc and lead, in addition to cadmium. Since smelters also commonly process relatively crude materials exposure to other metals such as chromium, arsenic, nickel, etc. cannot be eliminated as possible contributors to the observed effects. Synergistic effects between metals may also confuse the results from such studies.

Table 5 lists several studies dealing with point mutation. Drosophilia studies have been negative to date (Table 5) as have dominant lethal tests in mice (Table 4).

Although some of the above cited studies demonstrate mutagenic activity, at this point in time the relationship between a substance's mutagenic activity in lower forms and its potential as a human carcinogen is still not clear. Correlations between mutagenicity and carcinogenesis are quite good for certain classes of compounds and relatively poor for others. A major problem is that relatively few substances are recognized as unequivocal carcinogens for man. Chromosomal aberrations have now been noted in human leucocytes in response to a wide variety of diverse substances. The ultimate significance in terms of human health remains to be elucidated.

Carcinogenesis

This particular aspect of cadmium toxicology has received a number of recent reviews (IARC Monographs, 1973, 1976; U.S. EPA, 1977; NIOSH, 1976; Sunderman, 1977, 1978; and Hernberg, 1977).

Injection Studies

Animal studies have amply shown that the injection of cadmium metal or salts causes malignancies (sarcoma) at the site of injection and testicular tumors (Leydig cell interstitial cell). These studies are summarized in Table 6.

Injection site sarcomas arise from either subcutaneous or intramuscular administration. In comparison with other similar sarcomas in rodents they appear to be well differentiated (Heath, 1962), but give rise to distant metastases and may be permanently transplanted (Heath and Webb, 1967). There is now general agreement that studies demonstrating the production of sarcomas in rodents at the site of injection are not germane to cancer in man. A large number of chemical irritants and physical agents are known to cause sarcomas in rodents and they should not be considered as acceptable evidence of carcinogenicity for the human, except perhaps by the injection route.

Leydig cell (interstitial cell) tumor formation was briefly considered in a previous section of this evaluation. These tumors develop in rodents many months following the complete necrosis of the testis. Cadmium is only one agent

TABLE 4

Chromosome Mutation Studies on Mammalian Cells Exposed *In Vivo*

Author	Cells	Result and Comment
Shiraishi and Yosida (1972)	Human Leucocytes from Itai-Itai Patients	+ Increased chromatid breaks, isochromated breaks, chromatid translocations, dicentrics, and acentric fragments
Doyle, et al. (1974)	Sheep leukocytes	+ Reported in CAG Assessment
Shimada, et al. (1976)	Mouse cocytes	+ Reported in CAG Assessment
Deknudt and Leonard (1976)	Human Leucocytes from exposed workers	+ Chromatid aberrations and chromosome anomalies. Similar rate of effect in both high and low exposure groups. Chromatid breaks exchanges.
Bauchinger, et al. (1976)	Human leucocytes from exposed workers	+ Mixed metal exposure. (including Cd)
Bui, et al. (1975)	Human leucocytes	- Swedish battery workers - Itai-Itai patients
Gilliavod and Leonard (1975)	Dominant lethal test in mice	-
	Mouse spermatocytes	- No translocations.
	Mouse F_1 translocation test	-
Epstein, et al. (1972)	Mouse dominant lethal	-
Leonard, et al. (1975)	Bovine leucocytes	- Heavy mixed metal exposure (Cadmium 50x control levels) Exposure fatal to 6 of 15 animals.
Deknudt, et al. (1973)	Human leucocytes	+ Mixed metal exposure (including Cd)
Suter (1975)	Dominant lethal test in female mice	- Actual increase in living implants. No increase in dead implants.

TABLE 5

Point Mutation Studies with Cadmium

Author	Organism	Result
Shabalina (1968)	Drosophilia	-
Friberg, et al. (1974)	Drosophilia	-
Takahashi (1975)	Saccharomyces	+ Reported in CAG Assessment

TABLE 6

Animal Tumorogenesis Induced by Cadmium Injection

Authors	Species	Compound	Route	Tumor and Incidence
Haddow, et al. 1961	Rats	Cd containing ferritin	S.C.	Sarcomas (35%) Interstitial cell tumors
Heath, 1962	Rats	Cd powder	I.M.	Sarcomas (75%)
Heath and Daniel, 1964	Rats	Cd powder	I.M.	Sarcomas (90% and 75%)
Kazantzis, 1963b	Rats	CdS	S.C.	Sarcomas (60%)
Kazantzis and Hanbury, 1966	Rats Rats	CdS CdO	S.C. S.C.	Sarcomas (60%) Sarcomas (80%)
Haddow, et al. 1964	Rats	$CdSO_4$	S.C.	Sarcomas (70%)
Roe, et al. 1964	Rats	$CdSO_4$	S.C.	Interstitial cell tumors (55%)
Gunn, et al. 1963	Mice	$CdCl_2$	S.C.	Interstitial cell tumors (77%)
	Rats	$CdCl_2$	S.C.	Interstitial cell tumors (68%)
Gunn, et al. 1964	Rats	$CdCl_2$	S.C.	Sarcomas (41%)
	Rats	$CdCl_2$	S.C.	Interstitial cell tumors (86%)
Gunn, et al. 1967	Rats	$CdCl_2$	S.C.	Sarcomas (10%)
Knorre, 1970	Rats	$CdCl_2$	S.C.	Sacromas (13%)
Knorre, 1971	Rats	$CdCl_2$	S.C.	Interstitial cell tumors (40%)

Lucis, et al. 1972	Rats	$CdCl_2$	S.C.	Interstitial cell tumors (87%) Sarcomas (13%)
Reddy, et al. 1973	Rats	$CdCl_2$	S.C.	Interstitial cell tumors (80%)
Furst and Cassetta, 1972	Rats	Cd powder	I.M.	Sarcomas (54%)
Favino, et al. 1968	Rats	$CdCl_2$	S.C.	Interstitial cell tumors (100%)
Malcolm, 1972	Rats	$CdCl_2$	S.C.	Sarcomas (?) Interstitial cell tumors (?)

producing this effect in rodents, supra vide. Interstitial tumors do not differ morphologically irrespective of their mode of origin although those induced by cadmium exhibit more androgenic activity than those resulting from total vascular ligation (Gunn, et al. 1965). Histologically, the tumors are well-differentiated and composed of Leydig cells of relatively uniform appearance (Reddy, et al. 1973) and retain their steroidogenic characteristics. These tumors are androgenically functional (Gunn, et al. 1965; Favino, et al. 1968), although producing less testosterone than normal. The malignant potential of interstitial cell tumors is problematical: "The dividing line between hyperplasia and neoplasia is as indefinite as the rats studied and an even greater problem and one of vital concern in prognosis, is the distinction between benign and malignant tumors. At present, problably the only reliable criterion of malignancy is the presence of metastases" (Roe, et al. 1964). Cadmium induced interstitial tumors have never been reported to metastasize. The spontaneous development of interstitial cell tumors in rats varies considerably with the strain. Aged Fischer rats have been shown to have a very high rate (68 percent) of spontaneous interstitial cell tumor formation (Jacobs and Huseby, 1967). Malcolm (1972) has noted the development of these tumors in control animals from the weekly palpation during examination. Interstitial tumors of the testis are rare in man and account for less than 2 percent of all testicular tumors (Dixon and Moore, 1953). Out of a total of 49 cases reported in the literature only five were reported as being malignant. None of the 12 cases in the Army series, followed from 4 to 16 years had evidence of metastases or recurrence (Dixon and Moore, 1953). This tumor has yet to be reported in association with human exposure to cadmium.

In general, the simultaneous administration of zinc is protective against the formation of either sarcoma and/or interstitial cell tumor development (Gunn, et al. 1963b, 1964). However, zinc powder given intramuscularly fails to prevent formation when the inducing agent is cadmium powder (Furst and Cassetta, 1972).

Other Animal Studies

Several long term feeding and inhalation studies with cadmium have been carried out, but the induction of tumors has not been noted.

Schroeder, et al. (1964) has conducted lifetime exposure studies in Swiss mice. The animals were supplied with drinking water containing 5 ppm of cadmium acetate. Both males and females experienced some shortening of life span in comparison with the controls. The exposed animals had fewer tumors than the controls. Using rats at the same dosage they subsequently reported similar negative results and concluded that cadmium could not be considered carcinogenic in the doses given (Schroeder, et al. 1965).

Levy, et al. (1973) gave three groups of mice weekly doses (1.0, 2.0 and 4.0 mg/Kg body weight) by gavage for 18 months. No difference between exposed and control animals was noted in regard to general health or tumor incidence at 18 months. Similar experiments with hooded CB rats using doses of 0.2, 0.4 and 0.8 mg/Kg of cadmium sulphate weekly for 2 years were carried out by Levy and Clark (1975) with again no difference in tumor incidence in exposed and control groups. Decker, et al. (1958) reported on a rat study in which rats were supplied cadmium chloride in drinking water in the following concentrations: 0.1, 0.5, 2.5, 5.0, 10.0 and 50 ppm as cadmium. The highest dose group was terminated at 8 months because of appreciable stunting. Two animals from each of the other groups were sacrificed quarterly up to 1 year. There were no differences in body weight between control animals and those receiving up to and including 10 ppm. Nor were there differences in food or water intake or pathologic changes.

Anwar, et al. (1961) exposed eight dogs to 0.5 to 10 ppm cadmium (as cadmium chloride) for 4 years. Aside from a splenic nodule in a dog treated with the lowest dose, no tumors were observed.

Paterson (1947) carried out inhalation studies with cadmium oxide and cadmium chloride fume using rats. He used animals treated in the following way: 136 rats surviving the acute LD_{50} (800-1,000 min. mg/m^3); 100 rats surviving one-half the LD_{50}; and 200 rats exposed to approximately one-quarter the LD_{50} of cadmium chloride every 2 weeks for 6 months (12 exposures). Sacrifices were made periodically and the experiments were terminated 6 months after beginning exposure. No tumors were noted in the lungs. Apparently other organs were not examined.

Malcolm (1972) gave rats up to 0.2 mg of cadmium sulphate subcutaneously and up to 0.8 mg weekly by stomach tube for 2 years. In a third experiment, mice were given doses up to 0.02 mg/Kg of body weight subcutaneously at weekly intervals for 2 years. Except for a few sarcomas seen in the rats given subcutaneous injections and Leydig cell tumors (also seen in the controls) these studies were negative at the time reported. Several of the above briefly described oral intake and inhalation studies have been termed inadequate (IARC, 1976), apparently on the basis of the relatively small doses employed. Schroeder's work was specifically designed to simulate human exposure and for the most part the doses given seem realistic. Obviously, the doses were well below the maximum tolerable doses usually used today in attempting to establish the carcinogenic potential of various substances. Nonetheless, there seems to be a rather large volume of negative animal data.

Other Pertinent Studies

Koller (1978) has reported on the effect of cadmium exposure on tumor growth and cell-mediated cytotoxicity in mice inoculated with MSB-6, a MSV derived tumor cell line. A dose dependent inhibition of tumor growth was seen in those mice receiving cadmium. At 3 and 30 ppm dose levels, no inhibition of body weight accompanied tumor growth reduction, whereas at 300 ppm, there was a small inhibition of body weight gain. Cadmium exposed animals demonstrated significantly higher levels of cell mediated tumor cytotoxicity than controls. No data on the effects of cadmium upon the growth of non-viral-induced tumors has yet appeared.

Carcinogenesis in Man

Potts (1965) was the first to draw attention to the possibility of cancer in man as a result of cadmium exposure. Previously, Friberg (1950) had noted three cases of cancer among 17 deaths in alkaline battery workers. The sites were bladder, lung, and colon. While there was no control group this would not seem an excessive number of cancer deaths, i.e. 17.6 percent. Potts reported on the causes of death of eight men with at least 10 years exposure. Five of the eight died of cancer. Their ages, years of exposure and tumor sites follow (Table 7):

TABLE 7

Adopted from Potts (1965)

Age	Years of Exposure	Cause of Death
75	14	Carcinoma of prostate
65	37	Carcinoma of prostate
53	35	Carcinoma of bronchus
65	38	Carcinoma of prostate
59	24	Carcinomatosis

The remaining three men died from auricular fibrillation, bronchitis, and atheroma. Potts, while recognizing that the number of cases was very limited, felt that the association between cancer in man and cadmium should be "fully explored." Normally, one would not expect more than two cancer deaths out of the eight deaths observed.

Kipling and Waterhouse (1967) surveyed a group of 248 workers who had been exposed for a minimum period of 1 year to cadmium oxide. Twelve of these men had died and the causes of death ascertained. The twelve include the eight reported by Potts. They computed the expected number of cases by site which would have occured by chance and compared it against the observed. Their table follows (Table 8):

TABLE 8

From Kipling and Waterhouse (1967)

Site of Cancer	Expected	Observed	Probability of Occurrence
All sites	13.13	12	0.660
Bronchus	4.40	5	0.449
Bladder	0.51	1	0.398
Prostate	0.58	4	0.003
Testis	0.11	0	0.898

From the above it is obvious that for cancers at sites other than the four listed a total of 7.53 were expected (13.13-5.60), but that only two at other sites were observed. It is unclear as to why the number of expected prostate cancers is so small, i.e. 0.58, even adjusting for age. Cancer of the prostate is very common in elderly males and at least three of the four cases (Potts' cases) were elderly, i.e. 65, 65, and 75. Cancer of the prostate in the United States is the third leading cause of cancer death in males aged 55-74 and the second leading cancer cause of death in males over 75. The percentage of cancer deaths due to prostate cancer for these two age groups is 7.6 and 19.3

percent respectively. Slightly over 2 percent of all U.S. male deaths and about 10 percent of cancer deaths are from this cause. The long term incidence (death rate 13-14/100,000) trends for cancer at this site have not changed over the period 1940-1974. The death rates are similar for this site between England and Wales, 11.51/100,000, and the U.S., 13.90/100,000 (Natl. Cancer Inst. 1977). Thus, the expected figure of Kipling and Waterhouse seems about half of that anticipated based on England's national prostate cancer statistics. It is of considerable interest that the rates for cancer of the prostate in Japan, the country with by far the highest daily intake of cadmium, are the lowest for any developed country in the world, i.e. 1.93/100,000. This contrasts sharply with the rate for Sweden (18.33/100,000) which is the highest in the world. The Swedish daily intake and body burdens of cadmium are among the lowest yet reported (Kjellstrom, et al. 1978a).

Holden (1969) in a letter to the editor mentions two cancer deaths in cadmium workers (prostate, bronchus). He gives no denominator data. It seems possible that these cases were included in the previous survey by Kipling and Waterhouse.

Lemen, et al. (1976) conducted a retrospective cohort mortality study using reported causes of death among cadmium smelter workers who had achieved at least 2 years of exposure in the years 1940-1969. Ninety-two deaths were known to have occurred out of the employee cohort of 292 white males. Comparison was made between the observed number of deaths and that expected based on age and calender-time, cause-specific mortality rates for the total U.S. white male population. There was a slight deficit of total deaths, i.e. 92 observed vs. 99.32 expected. All this deficit is accountable by the extremely low number of deaths due to heart disease; only 24 were observed and 43.52 were expected, a difference significant at the $p < 0.01$ level. Twenty-seven deaths were observed as a result of malignant neoplasms and 17.57 were expected. This is significant at the $p < .05$ level. Most of this excess was accounted for by neoplasia of the respiratory system, where 12 were observed and 5.11 expected, a difference significant at $p < 0.05$. The risk of prostatic cancer was also elevated, i.e., 4 cases observed vs. 1.15 expected although this difference is not significant. When further consideration was given to the time interval since onset of exposure, a significant risk of prostate cancer was demonstrated (4 observed vs. 0.88 expected $p < 0.05$) 20 years after onset of cadmium exposure. It should be pointed out that Lemen's group was exposed to arsenic, a well-documented human carcinogen, and Potts' group to nickel, another generally accepted human carcinogen. These elements may account for the increased incidence of respiratory tract tumors discussed in the above studies. Kjellstrom, et al. (1978b) has reported preliminary mortality data for 269 cadmium-nickel battery workers and a control group of 328 alloy factory workers. Cancer deaths were not statistically different in the two groups, but the alloy factory workers were found to have an increased mortality from prostate cancer. Certainly the idea that prostatic cancer in man is somehow related to cadmium cannot be entirely discounted without careful industry wide studies. However, the prostate is an unusual site for an occupational cancer and other chemicals have not been suspected of causing cancer in this organ.

While of questionable relevance to the human prostate cancer question, Levy's (1973, 1975) specifically designed long term rodent studies failed to detect evidence of prostate neoplasia.

Humperdinck (1968) followed up eight cases of chronic poisoning previously reported by Baader (1952). Four had died, one of lung cancer. Out of 536 workers with some cadmium exposure he was only able to find five cases of cancer (including the one of lung cancer) and concluded that his data did not support a causal relation between cadmium exposure and cancer.

McMichael, et al. (1976) studied the mortality of workers from four rubber producing plants. The SMR was 94 for the full cohort. The standard mortality rates for all cancer sites was not elevated, but at some specific sites an increase was noted: stomach, 148; rectum, 116; prostate, 119; all leukemia, 130; lymphatic leukemia, 158; and lymphosarcoma-Hodgkin's disease, 129. Rubber plant workers are exposed to a great number of compounds including benzene, an accepted human carcinogen, and the relationship of these tumors to cadmium is highly problematical.

Kolonel (1972, 1976) has suggested that there may be an association between cadmium and renal cancer. He examined the incidence of cancer at several sites for persons with an inferred occupational history of cadmium exposure and in a control population. Cadmium exposure was based solely on job classification information provided on admission to a cancer research hospital. The only significant association was with renal cancer. He had expected to find an increased incidence of prostatic cancer, but none was detected. To help substantiate and refine the association he noted a four-fold increase in renal cancer among smokers with an occupation suggesting cadmium exposure in comparison to controls. Tobacco, as previously mentioned, contains appreciable amounts of cadmium. However, non-smoking, cadmium exposed workers actually were found to have less renal cancer than controls. This suggests that some other agent in tobacco smoke may be responsible, or that at most, smoking operates in some synergistic manner with cadmium. Obviously this is an extremely tenuous association. Among all the tumor sites specifically reported for cadmium workers, many of whom probably were smokers, the kidney has yet to be mentioned.

In summary, the available epidemiologic evidence does not suggest that cadmium can be definitely implicated as a human carcinogen.

CRITERION FORMULATION

Existing Guidelines and Standards

Numerous domestic official agencies, foreign governments, and private parties have suggested standards or limits for cadmium in various environmental media. The more germane of these are presented in Table 9.

TABLE 9

CADMIUM

Regulatory Standards, Limits, or Criteria for Human Health Protection

	Media		
Establishing	Air(Inhalation)	Water(Ingestion)	Food (Ingestion) Entity
OSHA (1974)	100 $\mu g/m^3$(1)		
NIOSH (1977)	40 $\mu g/m^3$		
EPA (1975)		10 $\mu g/ml$	
FDA (1978)			0.5 $\mu g/ml$(2)
WHO (1971)		10 $\mu g/ml$	
ACGHI (1977)	50 $\mu g/m^3$		
MEG/EPC (1977	0.12 $\mu g/m^3$	WH1-1.9 $\mu g/l$(3) WH2-0.7 $\mu g/l$(4)	
NAS/NAE (1972)		10 $\mu g/l$	
USSR (suggested)(5)		1$\mu g/l$	
CANADA (1968)		10 $\mu g/l$	
OHIO(6)		5 $\mu g/l$(streams)	

1. For cadmium fume. Limit for cadmium dust is 200 ug/m^3

2. Based on ceramic pottery and enamelware leaching solution test

3,4. EPC (estimated permissible concentration) WH1 is derived from the assumption that the maximum daily safe dosage results from 24-hour exposure to air containing the estimated permissible concentration in air, assuming 100 percent absorption and that the same dose is therefore permissible in the volume of water comsumed per day; WH2 is the estimated permissible concentration of the substance in water based on considerations of the safe maximum body concentration and the biological half-life of the substance

5. Krasovskii, G.N., et al. 1976

6. Lykins, B.W.,Jr., and J.M. Smith, 1976

Current Levels of Exposure

Section 1 of this document deals with general environmental exposure to cadmium. Food represents the major route of human exposure, with air contributing only a negligible amount to the total intake, except in tobacco smokers. Drinking water normally would account for less than 10 percent of the daily total absorption for the vast majority of the population. Percutaneous absorption is inconsequential.

It is recognized that approximately 100,000 Americans have potential occupational exposure to cadmium (NIOSH, 1976). The spectrum of occupational exposure varies from negligible to those situations producing acute and/or chronic toxicity and even death. While efforts are being made by those in occupational health to reduce exposure to a minimum and eliminate adverse health effects it must be recognized that no general environmental standard can prevent damage from overexposure in the occupational setting.

Special Groups at Risk

Persons with severe nutritional deficiency, i.e. calcium, zinc, protein, Vitamin C and D, etc., which may be aggravated by cadmium are conceivably at special risk, although human data concerning these effects are presently scant. Such a risk is obviously additive since these deficiences can in and of themselves be sufficient to cause disability and/or fatal disease. Obviously, persons in such precarious physiologic balance are particularly vulnerable to a wide variety of biologic and chemical hazards.

Some persons with diets that are adequate in terms of vital nutrients, calories, etc., but who subsist on otherwise skewed diets such as vegetarians or those eating unusual quantities of visceral meats, fish, or seafoods, which can contain rather large amounts of cadmium, may also be at increased risk. The additional risk to such population groups posed by an additional exposure increment from ambient cadmium remains to be assessed.

Basis and Derivation of Criterion

There is no doubt that cadmium is a teratogen in several rodent species when given in large parenteral doses. Doses of this magnitude (4-12 mg/Kg) would surely produce severe, if not fatal toxic symptoms in man. In the human only small amounts of cadmium cross the placental barrier (Lauwerys, et al. 1978). Only one report, from Russia (Tsvetkova, 1970), suggests any effect, i.e. low birth weight and "several children with rickets or dental trouble." Details are lacking in this report and it should not be construed as implicating cadmium without further data.

The studies of whether cadmium is mutagenic are inconsistent. The reports of chromosomal aberrations in both Itai-Itai patients and cadmium workers are conflicting. Dominant lethal studies have been negative as are tests for spermatocytic chromosome aberrations in male mice and their first-generation offspring (Gilliavod and Leonard, 1975). Studies of mutagenic activity in non-mammalian life forms have given inconsistent results.

There is no question that the injection of cadmium into rodents results in injection-site sarcomas and interstitial cell tumors of the testis. Sarcoma production in rats is a common sequela to the injection of irritants and could be regarded as a non-specific response to fibroblast injury. Interstitial tumors appear to result from the hyperplasia and metaplasia of tissue regeneration following vascular mediated testicular damage. There is no evidence that these tumors are malignant neoplasms, however, this does not refute the tumorogenic potential of cadmium.

The human evidence for the carcinogenicity of cadmium is conjectural, based on very small numbers, and confounded by exposures to other elements which are known to be human carcinogens. The reports on British battery workers and the work of Lemen, et al. (1976) suggest an increase in prostrate and lung cancer. These men were also exposed to nickel and/or arsenic, but in amounts of 1/100's-2/200's of cadmium exposure level. Kolonel's (1972, 1976) work confirmed neither of these sites, but suggested an association with renal cancer. This work is inadequate in that it assumes an exposure to cadmium based upon an occupational questionnaire. There have been no case reports of renal cancer in known cadmium-exposed workers. Cigarette smoking would appear to have a firmer association with renal neoplasia, rather than cadium. The geographic distribution of prostrate cancer (Japan, Sweden, USA) suggests that an inverse relationship exists to cadmium exposure. From the known mortality study data cited it might be argued that cadmium exposure reduces general mortality or is a potent protective factor against cardiovascular disease. The case for cadmium as a carcinogen is not persuasive when the existing data are critically reviewed, but it has been viewed by some as suggestive from the public health perspective.

It is not recommended that cadmium be considered a suspect human carcinogen for purposes of calculating a water quality criterion. However, the weight of evidence for oncogenic potential of cadmium is sufficient to be "qualitatively suggestive" and is not to be ignored from a public health point of view. The EPA Carcinogen Assessment Group has reviewed cadmium and their summary is included in the Appendices of this document.

The criterion is based on established health effects. The data implicating cadmium as a cause of emphysema and renal tubular proteinuria is firmly established. Emphysema has been reported only after airborne exposures and has been documented for both man and animals. It would seem to result from a direct effect upon lung tissue of which cadmium salts are known irritants.

There is evidence from occupational studies that the kidney is more sensitive to the effects of cadmium than the lung. In exposed workers proteinuria occurs in higher incidence and in a shorter time period than emphysema. It seems entirely justified to conclude that the kidney is the critical target organ.

It is generally accepted that the critical cadmium level at which renal dysfunction occurs is approximately 200 ug/g wet weight of renal cortex. Autopsy studies indicate that at present the average kidney concentration in non-smokers is approximately one-twelfth this level. In smokers the concentration is about twice as high, i.e. 30-39 ug/g.

Friberg (1974) has estimated that the critical level is reached at daily ingestion levels of 250-350 ug per day over 50 years. Since the average, non-occupationally exposed American probably does not have an intake from all sources exceeding 25-50 ug there would again seem to be a reasonable "safety-factor" of 5 to 12 in existence. While this is not the comfortable margin or many orders of magnitude usually recommended by toxicologists it should provide a margin of "safety" to the general public for the foreseeable future.

NIOSH (1976) recommends that workers should not be exposed to airborne cadmium at a concentration greater than 40 $\mu g/m^3$ as a time weighted exposure for up to a 40 hour work week. This standard is designed to protect the health and safety of workers over an entire working life time. Compliance should prevent adverse effects on the health of the worker. Several studies have indicated no adverse effects at levels of 31 and 16-29 $\mu g/m^3$ (Lauwerys, et al. 1974; Tsuchya, 1976). Effects of renal function (proteinuria) and a reduction in mean pulmonary function have been noted at levels of 66 $\mu g/m^3$ although some of these workers probably had experienced exposure, at least intermittently to cadmium fume at higher, but unknown concentrations. The limit of 40 $\mu g/m^3$ offers a greater, and "probably sufficient margin of safety" in comparison with the 50 $\mu g/m^3$ recommended by ACGIH (1977) and Lauwerys, et al. (1974).

From the figure 40 $\mu g/m^3$ it can be calculated that a worker might absorb about a 1000 μg during a work week, i.e. 40 $\mu g/m^3$ x $10m^3$ inhaled/day 5 days 0.5 (lung absorption rate). This is approximately 286 μg/day intake and 143 μg/day absorbed. To this the average daily intake from food and general environmental sources can be added, i.e. 10-50 μg. This suggests that an exposed worker may have an approximate intake of 300 μg/d and still be safe. However, a healthy worker may not be representative of the American population as a whole.

From Japanese dietary intake data where Itai-Itai disease is prevalent, and studies on the age-specific incidence of proteinuria, it is possible to estimate a no-effect level for ingested cadmium. In areas where Itai-Itai disease is most common, about 85 percent of the daily cadmium intake is derived from rice, the locally grown grain staple (Muramatsu, 1974). Nogawa, et al. (1978) have shown that the prevalence of tubular proteinuria, as measured by retinol binding protein excretion, in persons under age 70 does not begin to rise above that seen in control populations until the cadmium levels in rice exceed 0.40-0.49 µg/gm. The Japanese diet in the area of endemic Itai-itai disease and even in the homes of patients with the disease are precisely known (Friberg, 1974). Approximately 2100 calories are consumed daily, with carbohydrate accounting for about 1725 calories daily, which is equivalent to the ingestion of 430 gm/d. The no-effect level for Japanese can be calculated as follows:

$$\frac{430\text{ gm/d} \times 0.45\ \mu\text{g/gm (rice)}}{0.85} = 228\ \mu\text{g/day}$$

This Japanese figure is slightly below the estimate of 250 µg/day given by Friberg (1974) as an effect level. The no-effect level for a western European or American population with correspondingly larger body size would be expected to be somewhat greater (i.e., 301 µg/day).

The Working Group of Experts for the Commission of European Communities has estimated (Comm. Eur. Communities, 1978) that the threshold effect level of cadmium by ingestion at around 200 ug daily corresponding to an actual absorption of 12 µg/day. For smokers this estimate is reduced by about

1.9 μg to 10.1 μg which corresponds to an oral intake of 169 μg. Using a second approach based on metabolic modeling of the above type, this same group derived a threshold effect level of 248 μg daily when pulmonary absorption is negligible.

Using the data presented in this and preceeding sections of the document, it is possible to construct several exposure scenarios encompassing possible best-to-worse case exposure situations that might be domestically encountered:

Worst Case - Maximally Exposed Persons

Exposure Sources	Exposure	Cd Intake/d	Absorption Factor +	Cd Retention/d
Air-Occupational	*0.1 mg/m^3	714.0 μg	0.5	357.0 μg
Air-Ambient	400 $\mu g/m^3$	8.0 μg	0.5	4.0
Air-Smoking (three packs)	3.0 μg/pack	9.0 μg	0.5	4.5 μg
Foods	------	75.0 μg**	0.1	7.5 μg
Drinking Water	10 μg/l***	20.0 μg	0.1	2.0 μg
		826.0 μg		375.0 μg

* OSHA Standard for Cadmium fume

** Pahren and Kowal, 1978. Less than 1 percent of diets are expected to exceed this value

*** Section One. Less than one water supply in 300 exceeds this value

+ These absorption factors may be considered maximal for man

Average Case

Exposure Sources	Exposure	Cd Intake/d	Absorption Factor+	Cd Retention/d
Air-Ambient	0.03 $\mu g/m^3$	0.60 μg	0.25	0.150 μg
Air Smoking (one pack)	3.0 μg/pack	3.00 μg	0.25	0.750 μg
Food	----	30.00 μg	0.05	1.500 μg
Drinking Water	1.3 μg/l	2.6 μg	0.05	0.130 μg
		36.2 μg		2.530 μg

* Average for both sexes excluding drinking water (Section One)

+ These absorption factors are considered to be the most realistic available

Best Case - Minimally Exposed Persons

Exposure Sources	Exposure	Cd Intake/d	Absorption Factor	Cd Retention/d
Air-Ambient	0.001 $\mu g/m^3$	0.02 μg	0.25	0.005 μg
Food	------	12.00 μg	0.05	0.600 μg
Water	0.5 $\mu g/l$*	1.00 μg	0.05	0.050 μg
		13.02 μg		0.655 μg

* McCabe, 1974. This data indicates that 37 percent of Community Water Supplies had less than 1.0 μg Cd/l, which was the practical limit of analytic sensitivity at the time of his survey

From these scenarios it can be calculated that ingested water contributes relatively little to the daily retained cadmium entering the body i.e., 0.53, 5.1, and 7.6 percent respectively for the worst, average, and best cases. Water could become a significant contributor to all over cadmium intake and retention only if the secenarios are reconstructed by substituting the worst case water data for that in the average and best cases. However, even in the very unlikely event that such situations occur the total cadmium intake and retention remain comparatively modest i.e., 53.6 μg/d intake and 4.4 μg/d retained in the average case. The totals for the best case substitution are substantially less i.e., 32.02 μg/d intake and 2.605 μg/d retention. Therefore, it may be concluded that there are no circumstances in which ambient waters meeting current drinking water standards pose a threat to human health.

Based on the foregoing data and discussion it seems entirely justifiable to conclude that water constitutes only a relatively minor portion of man's daily cadmium intake. From the above analysis it is obvious (average case scenario) that drinking water contributes substantially less to human cadmium intake and/or retention than smoking a package of cigarettes daily. From this analysis it appears that a water criterion needs to be no more stringent than the existing Primary Drinking Water Standard (10 μg/l) to provide ample protection of human health.

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APPENDIX I

Summary and Conclusions Regarding The Carcinogenicity of Cadmium

Environmental exposure to cadmium occurs by several routes. The estimated cadmium retention of an individual from food is about 3.0 μg/day; water, 0.09 μg/day; and air, 0.15 μg/day. People smoking five cigarettes per day have an additional retention of about 0.35 μg cadmium. The production of refined cadmium metal is a potential source of cadmium for local surface water. In drinking water the average level of cadmium is on the order of 1 μg/l, but may be as high as 10 μg/l.

Cadmium has been reported to cause chromosomal or mitotic aberrations in mammalian cell culture lines. *In vitro*, it induces cellular transformation and also enhances transformation of virus-infected mammalian cells. These tests are known to be highly correlated with oncogenicity. Further it has been shown to produce adverse effects in both man and experimental animals, eg. pulmonary emphysema and renal tubular damage. In human tissues, the concentration of cadmium increases up to the age of 50 years.

There is suggestive evidence from four occupational studies of highly-exposed workers that inhalation of cadmium may be associated with prostrate cancer in humans. Subcutaneous injection of soluble cadmium salts in both rats and mice caused interstitial cell tumors of the testis. However, orally-administered cadmium has failed to induce carcinogenic responses in rats and mice, perhaps because it is not absorbed readily from the gastro-intestinal tract.

It is, therefore, possible that cadmium in drinking water and fish could induce prostate cancer in humans. A water quality criterion based on lifetime risk of 10^{-5} is calculated using the data of Potts, (1965) for proportional mortality in alkaline battery factory workers with the assumption of a 50 percent absorption for inhaled cadmium, 10 percent absorption for ingested cadmium, a fish bioconcentration factor of 17.0, and other assumptions common to the water quality risk assessments. The result is that the water concentration should be less than 0.28 micrograms per liter in order to keep the lifetime risk below 10^{-5}.

Quantitative Risk Estimates for Carcinogenicity of Cadmium (Cd)

From the CAG document [1], the lifetime risk to atmospheric Cd is $R=(1.879)\ (10^{-3})\ (X)$, where X is the lifetime average daily air concentration in ug/m^3.

The Cd intake from a concentration of 1 ug/m^3 of Cd in the air is:

$1\ ug/m^3 \times 24\ ug/day = 24\ ug/day$ assuming 100 percent absorption

Studies show that 50 percent absorption may be more realistic, therefore the Cd intake is:

$$24\ ug/day \times 0.5 = 12\ ug/day$$

If this amount of Cd were absorbed from the typical ambient water exposure pathways (assumed to be 2 liters/day of drinking water, and 0.0187 kg/day of fish products) with

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a fish bioconcentration factor of 17, the resulting level of Cd in ambient water, C, would be:

$$12\ \mu g/day = C_1\ (2 + (0.0187)\ (17))$$

$$5.117\ \mu g/l = C_1$$

In order to absorb this much from water and fish (assume 10 percent absorption from the GI tract), the water concentration corresponding to 1 $\mu g/m^3$ of air would have to be 51.77 $\mu g/l$. Therefore, 1 $\mu g/m^3$ in air produces a risk equivalent to a water and fish consumption resulting from 51.77 $\mu g/l$ in the water. The air level giving a lifetime risk of 10^{-5} is:

$$X_1 = 10^{-5}/(1.879 \times 10^{-3}) = 0.532 \times 10^{-2}\ \mu g/m^3$$

This corresponds to a water level of

$$C = 51.77 \times 0.532 \times 10^{-2} = 0.2754\ \mu g/l$$

$$\simeq 0.28\ \mu g/l$$

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1. Assessment of Carcinogenic Risk from Population Exposure to Cadmium in the Ambient Air. Carcinogen Assessment Group report May 19, 1978.